ANNALS of ALLERGY

Published by the
American College of Allergists

Volume 3 May-June, 1945 Number 3

A BRIEF CRITIQUE OF PSYCHOSOMATICS

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"Man is said to be a compound of soul and body. However proper this language may be in religion, it is not so in medicine. He is, in the eye of a physician, a single and indivisible being, for so intimately united are his soul and body that one cannot be moved without the other. The actions of the former upon the latter are numerous and important. They are causes of many diseases; and if properly directed, they may easily be made to afford many useful remedies. . . .

"I am aware, gentlemen, that the science which I am now recommending to you is an unpopular one, and that it is often treated as chimerical and uncertain. While it bore the name of metaphysics, and consisted only of words without ideas, of definitions of nonentities, and of controversies and the ubiquity and other properties of spirit and space, it deserved no quarter from the rational part of mankind; but the science I am speaking of is as real as any of the sciences that treat upon matter, and more certain and perfect than most of them. As a proof of this I need only call your attention to the innumerable changes that have taken place in the theories of every branch of what is called physical science, and to the improvements which have taken place in each of them within the last two thousand years. Very different is the state of ——— the science of the mind. Most of the leading opinions and observations of Locke, Condillac, Hartley, and Reid may be found in the writings of Aristotle and Plato. . . . The reason of this certainty and near approach to perfection is obvious. The mind is the same now that it was in the time of those illustrious Greek philosophers, and, of course exhibits the same phenomena in all of its operations to the moderns that it did to them."

THESE excerpts from an introductory lecture to medical students given in 1805 by Benjamin Rush[10], a teacher of general medicine, illustrates that psychological and philosophical psychiatry has undergone no changes in essential content for many years.

However, under the impetus of magical thinking by clinicians of the psychoanalytic school, physicians have been roused, as a matter of defense, from a lethargic attitude toward the importance of domestic, moral, social, and other personal components as concomitants or etiological factors of disease, to an awareness that acknowledgment at least must be made that the physicians "knew it all the time."

Presented at the Southwest Allergy Forum, New Orleans, April 9, 1945.
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It is questionable that modern psychological psychiatry is actually more "modern," or has added any pertinent information to its body of knowledge for many years.

Draper[1] has expressed this fact in a recent article:

"If we examine closely the structure of organismic unity which doctors nowadays seem to be striving so hard to preserve for the individual, we may find perhaps that its division resides in a contemporary medical attitude and not within the animal at all."

And again:

"In our correct professional phrasing, we are by now, no doubt inexorably committed to the word "psychosomatic." The precariousness of the term, however, lies in the fact that its hoped for symbolic connotation of unity may be lost in the false belief that two separate parts in man actually do exist. The only way man has been able to deal with the imponderable forces which he has sensed to be present is by abstract words or symbols. There is, however, a peril in this process, the danger that the possible, wished for, or probable reality for which a given abstraction stands may be obscured by the poignant connotation of the symbol itself, which then takes on the fixed nature of reality."

The term "psychosomatic medicine" is a very unfortunate addition to our unscientific semantics. Loose usage of the term is a threat to modern medical education. It would channelize potentialities and curb the natural efforts of mankind toward better understanding of illnesses that do not belong to the realm of medicine per se. There is no such entity as "psychosomatic medicine" any more than there is "psychosomatic sociology," "psychosomatic philosophy," "psychosomatic politics," or "psychosomatic mysticism."

There are no ontogenetic influences that possess potentialities of producing a reactive organic response from the phylogenetic pattern of an organism so as to characterize the response as being something on the order of a clinical syndrome which should be placed in the category of a psychiatric disability.

It is not within the professional realm of the physician to bear the burden of the connotations involved in the tenets of "psychosomatic medicine." All illnesses that may be the result of emotional conflicts are on a reality basis *to the sufferer.*

It is important that the physician continue his traditional orientation toward humanity and that he realize that current environmental factors responsible for the production of symptoms do not belong in his specific domain. For some reason, the physician is always a specialist in his own way. He is first a physician, second, a politician, gentlemen farmer, et cetera, and if he lets the latter interests become too dominant, he no longer is really a qualified physician. The physician was then, is now, and shall be afterwards, a person who attends primarily to disturbances of the "physic."

This does not mean that he should not be a counsellor, or that he should ignore emotional problems in his patient. He should be informed of them, and advice should be given the patient regarding changes that might help, but the major proportion of symptoms that occur as the result of personal relationships involve a moral conflict. The physician-priest relationship was severed gradually many years ago. It would be hazardous for the physician to assume the responsibility of moral guidance, especially since he severed relationship with the priest, and not vice versa.

Advice regarding activities of the patient as to unhygienic attitudes are in order, but the assumption of the role of moral interpreter, with ritualistic components, as manifested by some psychiatric techniques, is not of teleological therapeutic value.

The physician who has patients with reality conflicts that produce allergic or other symptoms may deal with the problem to the best of his ability, but the patient's neighbor who is not professionally trained in anything, might, and often does indulge in counselling, solicited by the patient, with the materialization of excellent results.

There is no academic training that would be apropos. There is no educational program that would be effective so far as "psychogenic" allergic symptoms are concerned; because such a program would be a symptom tantamount to, or worse than the psychogenic allergic manifestations in those people so constituted to react in such a way.

Indulgence in rationalizations of mother, father, sister, brother, grandmother, grandfather, aunt, uncle and cousin relationships as the etiological basis of any chronic ailment is only an indication of a psychiatrist, psychologist, preacher, or like animal in trouble himself.

The herd instinct is a biological expression, not of protoplasm, but of many protoplasms that make up life. Current attitudes would indicate the inevitability of a temporary internationalism, but there is no reason to believe that the amazing modern inventions will alter the cycle of fundamental biological processes.

The psychological aspects of allergy may be dealt with by the allergist much as such problems that have existed and have confronted the family physician for ages. The "psychic" component of the autonomic nervous system disturbances is still in the realm of that wherewithal in which the unknown continues to be the unknown.

Shock therapy in the affective psychoses and in certain types of schizophrenic reactions has effected striking symptomatic improvement. It is likely that scientific studies enacted upon the basis of these results will some day give us enlightenment regarding these most malignant and serious disorders.

The results of prefrontal lobotomy on some special cases is another indication of latent scientific progress in that branch of psychiatry.

Much time could be consumed in the elaboration upon the thesis of

Benjamin Rush, in which he was of the opinion that Plato and Aristotle had fairly well exhausted the fountain of knowledge so far as the human "mind" was concerned.

During the latter part of the 19th century and the first part of this century a very potent and somewhat prolific school of magical thinking came into existence. This school of dogmatists was founded by Sigmund Freud, who became aware of the fact that physicians were not sufficiently cognizant of the importance of reality factors of a personal nature on the influence and production of certain disorders. He did not announce the discovery as such, but instead, created a term, "unconscious," and endeavored to place a premium upon this category. The term was "catchy," and as a result, psychiatrists who supposedly have acquired special ability to deal with this mystical something, have, in the opinion of many, become magically bestowed with unusual conditional abilities. However, now, really, it is believed by most that physicians "knew it all the time."

An elaborate system of "neologisms" has evolved from this school of magic. Examples are: superego, id, ego, repression, sublimation, displacement, oedipus complex, castration complex, penis envy, anal sadism, death instinct, identification, ambivalence, pleasure principle, lay analyses, analysand, transference, counter-transference, polymorphous perversion, passive feminine traits, and dream interpretation. There are many others.

The psychiatrist, from about 1920 on, was something of an outcast, or at least a very "unfortunate creature" unless he had became subjected to the ritual of psychoanalytic training. In the opinion of the psychoanalyst, no person was capable of understanding the psychiatric disorders unless he had been "analyzed" by a qualified training analyst who had met the requirements consisting of a careful scrutiny of the dogmatists.

It is interesting that such a furor occurred, after the founder of the psychoanalytic "school" became aware of emotional factors in the production of illness. Actually, the furor came about as the result of Freud's elaborate delusional system, developed in the effort to explain many very simple phenomena.

The rationalizations and exploitations of the psychoanalysts in the treatment of emotional problems is striking. They extended their claims to cures of such conditions as migraine, essential hypertension, eczema, stuttering, transvestism, hay fever, the common cold, asthma, morphine addiction, sexual perversion and even schizophrenia.

It is no wonder that physicians in other fields of work and that lay persons temporarily succumbed to belief and credence in such a marvelous "psychology." However, there is no doubt but that psychoanalytic technique has never cured a single case of the above-mentioned disorders.

The peripatetic philosophers of ancient Greece would throw both hands up, shake their heads, and walk away if permitted the opportunity of listening to the exchange of words during a psychoanalytic session between the "analyst" and the patient.

There was a "devil neurosis"[4] in the 17th century, but, undoubtedly wheals, eczema, asthma, hay fever, migraine, and blushing, and goose flesh all existed at that time.

There was the case of little Hans[5] who was afraid of horses in 1905, but there are many cases of little Johnnies who are afraid of automobiles and airplanes today.

Freud's explanation of little Hans' fear was that he was afraid of horses because of his incestuous wishes that he had toward mother. The horse was a symbol of father. This is only one example of the innumerable magical explanations of phenomena offered by the psychoanalysts. Modern studies have objectified magical thinking of primitive people. The dogma of psychoanalysis should likewise be objectified.

Lewis[8], in "Review of Psychiatric Progress 1944," considers Hellier's[7] discussion of dermatologic entities with emphasis upon psychosomatic components as being an important step. Hellier states that many cases of eczema, rosacea, falling hair, lichen planus, hyperidrosis, and warts have a predominance of psychogenic origin. He is of the opinion, however, that these reactions occur only in hypersensitive skins that overreact.

Is it remarkable that one would blush, if one had a tendency to blush, when confronted with a situation that caused blushing? Is it remarkable or even more than ordinary if one's skin has a tendency to epithelialization, that it epithelializes when subjected to epithelializing stimuli?

An example of influence of psychoanalytic thinking occurs in Hellier's explanation of rosacea that occurred in a spinster after her father's death. She sat up with him almost constantly for six weeks before his death. He then died. She developed rosacea which was supposedly a symbolic expression of shame (blushing) because of her guilt over her unconscious wish that her father would die. Is it possible that fatigue of six weeks' constant attendance on her father could have played any part in this skin disturbance? The patient got well after Hellier pointed out her unconscious guilt (according to him)—but she also undoubtedly got a long-needed rest.

Dunbar[2] cites many cases in which she contends that fractures, hypertension, coronary disease, arthritis, and almost every type of allergic disorders have specific psychic components.

French[3], upon the basis of a study of a few cases of asthma, has concluded that the asthmatic attack is precipitated by an external situation in which there is a threatened loss of security relative to a mother figure. The asthmatic wheeze to him is on the order of a stifled cry. In his cases he found that the parents overprotected the child to hide their guilt over an inner desire not to have the child. He recommends to parents, less solicitation of these children, and to the children, a more independent attitude toward the parents.

Wilson[12] believes that hay fever (after his analysis of seven cases) is the result of inadequately repressed olfactory sexual impulses. It has

something to do about man taking the upright position, and the nose getting too far from the ground. His patients were from Victorian families who changed the child's interest from the genitals to body excretions.

Saul[11] states that the common cold, hay fever, and allergy in general are manifestations of suffered intensification and frustration of passive receptive wishes with a strong oral component. Dreams presented by his patients, according to his interpretation, showed strong wishes for help from others. He states that colds would dramatically disappear when the patient acquired insight, or when frustration was alleviated. It is his opinion that colds and hay fever are perhaps closely related if not identical. However, no smears of the nasal mucosa were studied by him on any of his patients.

Fromm-Reichmann[6] has concluded that migraine is caused by repressed hostility toward a loved one in which the patient is not consciously aware of it. She states that it occurs in families who do not permit children to fight each other. The head is chosen as the site of pain because it is a symbol of intellectual rivalry. (If this is not magical thinking, then the primitive who poured water over rocks to produce rain was an intellectual genius!)

It would seem to be the tendency now to place most not understood clinical syndromes into the realm of "psychosomatic disorders."

Lipkin and Sharp[9] supply the following list:

"Cardiovascular neurosis, certain cases of hypertension, Raynaud's hyperventilation syndrome, many cases of asthma, cardiospasm, aerophagia, hyperacidity, anacidity, peptic ulcer, pylorospasm, biliary dyskinesias, mucous colitis, spastic and atonic constipation, ulcerative colitis, enteroptosis, urinary frequency, sexual disturbances, menstrual disturbances, neurodermite, urticaria, angioneurotic edema, eczema, certain cases of arthritis, certain types of headache, migraine, anorexia nervosa, and even obesity."

Let us not forget that general paresis was at one time similarly categorized.

Numerous writers have attempted clarification of clinical disorders being emotional, structural, or a mixture of both. Such classifications are essentially very loose and ill-defined.

There are many examples of physiologic reactions to emotional stimuli, and many theorize that these responses over a sufficient period of time will produce irreversible pathology. However, it remains to be proved that the responses that resulted in pathological changes were ever at any time physiological. Hypertension is a good example of this. The hypertension produces alterations in the arteries that became irreversible. But, was the hypertension that produced the arterial changes ever physiological?

There are writers who state that leukocytosis occurs on an emotional basis. Basal metabolic rates supposedly are altered by the emotions. The skin temperature drops in some people when disturbing subjects are discussed.

Treatment suggested by Lipkin consists of suggestion, catharsis, relax-

ation therapy, prescribed exercise, persuasion, psychoanalysis, distributive analysis, and group psychotherapy.

Psychosomatic medicine is being pushed by the psychoanalysts who have ready magical explanations for symptoms that cannot be explained as yet upon physio-pathologico-biological scientific grounds.

It is morbidly amusing to read the psychoanalytic and other psychologic literature pertaining to schizophrenic psychoses written in the pre-shock treatment era. One would really have difficulty in differentiating the patient's "material" from the analyst's "interpretations."

The psychoanalytic technique is nothing more than a relationship between the physician and patient (if the analyst is a physician), in which both the patient and analyst indulge in mutual fantasies toward each other. The procedure finally terminates when they tire of each other or when the patient's funds are exhausted. The pseudotherapeutic results consist of an induced delusional mosaic in the patient. The analyst had the delusions before the procedure was started. It is so to speak something on the order of a folie á deux.

This is not to minimize the influence of conflict situations in the production of allergic and other clinical symptoms. Undoubtedly such phenomena do occur—but they do so just as any added strain, or worry, or other reality situation would aggravate a manifest disease process. This is no new discovery and hardly deserves any special terminology for its description. Psychiatry, the so-called "Cinderella of Medicine," is permitting itself to be overrated. It has its place in medicine, but the dichotomy of mind and body is dangerous to science.

The psychiatrist has no specially pertinent information to impart to the allergist. Every allergist knows, just as every other physician knows, that the physician-patient relationship, as per the Hippocratic Oath implies that the doctor may make an appraisal of the intimate personal information obtained.

Advice to patients relative to any reality problems or conflicts that might be enhancing his allergic symptoms does not spring from information given through the discovery of a psychiatrist. It is the *sine qua non* of the physician as a part of the art of medicine.

It is important to stress to medical students that a careful history, with special inquiry regarding the possibility of emotional problems, be obtained. Evaluation of the information is not difficult. Errors in interpretation are more likely to occur on the "psychosomatic" rather than the biologic side.

Factors in reality that add to strain in constitutionally predisposed people who suffer with allergic conditions may, theoretically, in some instances provoke an attack. Even this remains to be scientifically proved.

The famous case of Prince is frequently quoted, in which sneezing occurred in a patient with hay fever sensitive to roses when shown a paper rose. This is not pertinent, because it was not shown that the attack of sneezing was an attack of hay fever.

Conditioned reflexes are definite entities and it is normal for one to respond with defense mechanisms to irritating or danger situations. However, what would be proved if a man who was sensitive to ragweed, and who knew what a ragweed looked like, sneezed when confronted with an artificial ragweed that looked like the real McCoy?

Would Prince's patient have sneezed at the artificial rose, had he not known that he was sensitive to roses?

Some practical points are herewith given, not with the idea of being informative, but more as a space filler for the paper.

In the examination of children, to discover the existence of a pertinent emotional problem, careful inquiry should be made into the matter of adjustment between the parents. If the inquiry does not call attention to and aid in the maladjustment, treatment of any sort will only serve to make matters worse.

In the adult in which an emotional conflict is discovered, it is well to determine the nature of the conflict.

Is the problem on a moral basis? e.g., does the patient have an illicit affair? Has he cheated on his income tax report? Has he borrowed money from an opulent relative and deliberately failed to make payments on the debt? Has he been padding his expense account? Has he spread malicious gossip about a competitor? He should be asked very frankly if any moral problems exist. Expression of the fact to the physician may or may not help; but again, attention is called to the fact that such might be a factor in the illness and may bring the matter to a focus in reality and the patient sometimes will take steps to correct the situation.

Is the emotional problem arising out of the person's inadequacy? Frequently such is the case. The patient is aware of the fact, but had not connected it with the presenting symptoms. When such is found to be true, the patient should be frankly told of the situation. Improvement depends upon the ability of the patient to adjust to the passive acceptance of an altered status and changed evaluation of himself. Some cannot make this adjustment. No one actually knows the reason why.

Is the emotional problem just an external situation, incidental, but inevitable, that is really overwhelming because of being a threat to the person's health, security, or other attributes of happiness? If so, nothing can be done until the external situation is altered.

This presentation has been made in the interest of medicine, with the concept that psychiatrists have no more information as to correction of social conflicts than do many other people. It is also presented in the interest of psychiatry to emphasize the above fact.

It is an extremely common, though embarrassing occurrence for the psychiatrist, after introduction, to have the person say, "Oh, you're a psychiatrist! I'm glad to meet you. I've always wanted to be psychoanalyzed. Let's go over here and sit down. I want you to psychoanalyze me right this minute."

Unfortunately, this impression and overestimation of the psychiatrist has become rather prevalent, and I'm afraid that the psychiatrist has unwittingly permitted it to be brought upon himself.

The psychiatrist is just a physician interested in the diagnosis, prognosis, further understanding, and treatment of disorders with clinical symptoms that places the patient in the category of a psychiatric disturbance.

There are no convincing reports in the literature of any allergic patients having received any more relief from psychiatric treatment than should have otherwise occurred from wise counseling with the allergist.

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Urticaria Following a Dental Silver Filling. Marcow, H.: Dental Outlook, 31:148, 1944.

The author reports this case of sensitivity to mercury or quicksilver used as dental fillings. The urticaria was present daily with its onset being noted immediately following a visit to the dentist. She experienced complete relief on the removal of all silver fillings. After the removal of each silver filling, there was a flare-up of urticaria for several hours. The contact test with mercury was immediately followed by a large area of urticaria over the test site.

The Mycotic Flora of the Oral Cavity in Normal and Pathological Conditions. Ottolenghi, R.: Dental Items, 66:134, 1944.

The author collected samples for culturing from the oral cavities of 100 patients affected with various dental disturbances. These samples were cultured in selective media, with positive findings in ten patients. Identification of the growth was accomplished by its cultural and microscopic characteristics, by hanging drop preparations and by carbohydrate fermentation patterns. The fungi were divided as follows: saccharomyces hominis, monilia (Zeilanica Castellani) (two cases), aspergillus herbariorium, sporotrichum, monilia undetermined (three cases), penicillium glaucum, and saccharomyces glomerolatus.

EXPERIMENTAL APPROACH TO ORAL TREATMENT OF FOOD ALLERGY

II. Immunologic Properties of Food Propeptans

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THE first paper in this series dealt with the chemistry of food propeptans. Food propeptans are food digests derived from the individual foods through prolonged digestion with hydrochloric acid and pepsin, followed by some slight additional digestion with trypsin. Thus, these preparations contain all the protein cleavage products such as the proteoses, peptones, subpeptones, simple peptids and amino acids, but no native protein.†

In the present communication—the second in the series—an attempt will be made to describe the immunologic properties of food propeptans.

Today, as is well known, distinction is made between two outstanding methods of anti-allergic treatments: hyposensitization and de-allergization (Urbach and Gottlieb).[10] The term hyposensitization designates the procedure by which the allergic organism is given small quantities of antigen in repeated and usually increasing doses at intervals of one or more days. Subsequent administration of an anaphylactic dose will be tolerated without manifest symptoms, although the lungs (in the lung perfusion test) and the uterus (in the Schultz-Dale test) are still anaphylactic. Therefore, the clinical insensitivity can be explained only on the basis of an excess of free circulating antibodies.

The term de-allergization designates the therapeutic measures by which, through the appropriate administration of antigen, the antibodies are neutralized or otherwise rendered incapable of reacting. In this manner, the principal shock tissues or the entire organism are rendered insensitive for a certain length of time or permanently.

In this paper, animal-experimental evidence will be adduced to demonstrate that propeptans lead to de-allergization—i.e., that propeptan therapy converts the organism from a state characterized by a high antibody titer to one in which the antibody level is normal. However, depending on quantitative and timing conditions, the de-allergization may be partial and temporary, complete but temporary, or complete and lasting.

On the other hand it will be shown that parenteral administration of food proteins while resulting in a clinical state of temporary hyposensi-

From the Department of Allergy, Jewish Hospital. Expenses for this work were defrayed in part by a grant from the Allergy Research Foundation, Inc., Philadelphia, Pa.

Sequel to "Experimental Approach to Oral Treatment of Food Allergy. 1. Chemistry of Food Propeptans." Erich Urbach, M.D., George Jaggard, B.S., David W. Crisman, V.M.D., Ann. Allergy, 2:424, 1944.

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†Food propeptans are in themselves entirely free from protein; however, for reasons stated elsewhere in this paper, glycyrrhiza is added to the propeptans intended for therapeutic use. This saponin contains 1.4 per cent protein nitrogen. Pure food propeptans for analytic or experimental purposes will be supplied by Dalare Associates, 2300 Locust Street, Philadelphia 3, Pa., on request.

tization does not deprive the shock organs of the antibodies, thus rendering the organism clinically sensitive again shortly after the hyposensitization treatment has been stopped.

After reviewing the literature on the antigenicity of the cleavage prod-

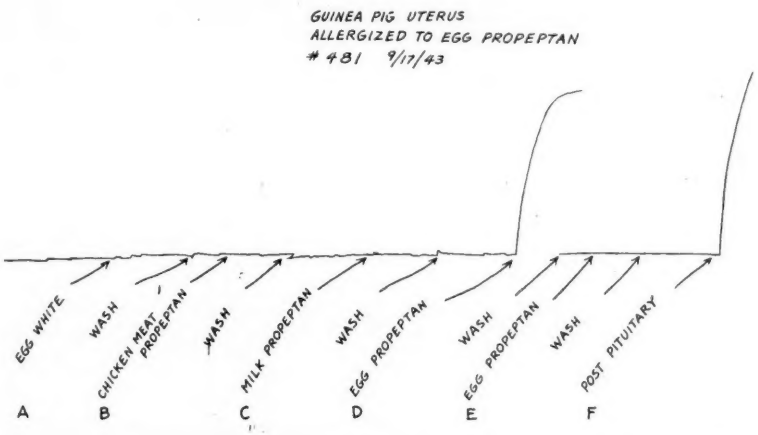

Fig. 1. Schultz-Dale test performed upon the uterus of guinea pig No. 481 allergized to egg propeptan. There was no reaction upon the additional egg white, chicken meat propeptan, or milk propeptan; however, the addition of egg propeptan resulted in a violent reaction. There was no reaction to a second portion of egg propeptan proving that the first reaction was specific for egg white. The final reaction was the result of posterior pituitary extract added as a check on the sensitivity of the uterus.

ucts resulting from the action of enzymes on protein, up to the year 1919, and on the basis of his own experimental work, Fink[3] arrived at the conclusion that it was most unlikely that the proteoses had any antigenic property. However, Landsteiner[5] succeeded in demonstrating that animals sensitized with digestive cleavage products of egg albumin responded to a re-injection of the same substance with characteristic and fatal anaphylactic symptoms. Urbach and Kitamura[5] were able to allergize guinea pigs by means of oral as well as parenteral administration of type-specific propeptans. This was demonstrated both by the anaphylactic experiment and by the Schultz-Dale test on a specifically sensitized uterus. Lastly, Cooke et al.[2] have reported sensitization of guinea pigs to Berna peptone.

All this would seem to establish the fact that the cleavage products of proteins possess anaphylactic properties. Furthermore, the senior author[8] has demonstrated the strict type-specificity of propeptans. The uterus of a guinea pig, sensitized with hen's egg propeptan, responds with contraction to hen's egg propeptan alone, showing no reaction whatsoever to administration of hen's egg white.

The high degree of the specificity is revealed by the fact that even propeptans, derived from hen's meat, fail to elicit any kind of reaction (Fig. 1). The type-specificity of food propeptans, as demonstrated by the

Schultz-Dale test (generally recognized as the most accurate and dependable procedure), conforms perfectly with our experimental findings in man. In this connection, we[8] should like to call attention to the case in which preliminary administration of egg propeptan inhibited the appearance of an allergic eczema when egg white was applied to the eyelids, or of an allergic rhinopathy following the introduction of egg white tampons into the nostrils; yet the appearance of these allergic responses was not inhibited when the patient, believing that she had received egg white propeptan, had in fact been given hen's meat propeptan. Similarly, in a case of asthma due to peas, the patient was able to eat quantities of peas with impunity, provided the specific pea propeptan was taken before the meal; but a severe attack was the result when the same quantity of lentil propeptan was substituted for the pea propeptan, without the patient's knowledge. Many similar instances could be cited from the literature and our own experience.

Thus, clinical observations and experimental findings alike demonstrate the type-specificity of the propeptans; and this would seem to establish the experimental and theoretical grounds for recognizing the value of propeptans in the diagnosis of food allergy. We shall now attempt to present conclusive animal experimental evidence of the therapeutic efficacy of the propeptans.

As is well known, Besredka[1] demonstrated that pre-administration of a given antigen whether subcutaneously, intravenously, intrathecally, rectally or orally affords complete protection against what would otherwise be a fatal dose of allergen. This is the basic principle involved in the procedure known as specific skeptophylaxis. The senior author[13] subsequently succeeded in showing that instead of giving the antigen itself (e.g., egg white), the corresponding propeptan (egg propeptan) may be advantageously used. The great advantage of substituting the type-specific food digest for the food antigen lies in the fact that both in humans and in animals, the degree of hypersensitiveness is not uncommonly so high that even minute quantities of the food in question may bring on very severe anaphylactic symptoms.

In the present study, we performed extensive experimental studies to redetermine conditions under which guinea pigs, sensitized by the intraperitoneal or subcutaneous route can be protected against the effects of a lethal anaphylactic shock-dose by type-specific propeptans administered intravenously or by mouth.

For each experiment, we used twenty virgin guinea pigs, weighing an average of 280 gm. and kept on an acid diet throughout, consisting of 7 gm. of rolled oats, 5 gm. of whole-wheat bran, 10 gm. each of potatoes, beets and hay daily. This is necessary, for animals given a diet of green fodder which is alkalizing are difficult to sensitize (Sulzberger and Mayer[9]). Parenteral allergization to egg white is readily achieved within three weeks by an intraperitoneal or subcutaneous injection of 0.1 c.c. of 50 per cent

egg white in saline. However, if the animals are to be sensitized to milk, meat, spinach, flour and other food proteins, it is advisable to inject 2 c.c. of skimmed milk, beef, flour, et cetera, together with 0.02 c.c. of alum precipitate, subcutaneously. The animals then show a high degree of hypersensitiveness after forty-three to forty-seven days. Needless to say, each individual preparation must be carefully checked to rule out any possible toxic action or tendency to evoke a nonspecific reaction on the uterus in the Schultz-Dale test. A preparation may be classified as nontoxic, when an intravenous injection of 4 c.c. of a 10 per cent digest is tolerated perfectly by the animal. Furthermore, it is necessary to perform preliminary experiments on a number of animals from each group, in order to determine the minimal lethal dose (M.L.D.) required for each series of experiments. The minimal lethal dose varies, depending on the animal's strain and weight, diet and the season.

Sensitization by the oral route is facilitated considerably by the addition of the saponin glycyrrhiza to the food protein. Glycyrrhiza increases the allergizing properties of the antigen manyfold because of better resorption resulting from its action in dissolving intestinal mucus (Urbach[10]). Another way to expedite sensitization is to introduce 1 c.c. of 25 per cent alcohol into the animal's stomach by means of a catheter before administering the allergic food to which the animal is to be sensitized. We have found this method, which was introduced by Hajos[4], to be highly effective.

ORIGINAL EXPERIMENTS

Twenty guinea pigs were allergized by means of an intraperitoneal in-

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Experiment 1

Guinea pig No. 778 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later, the following treatment was instituted.

Treatment.—Five intravenous injections of Egg Digest* at ten-minute intervals.

Injection 1.—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Slight bristling

Three hours after the last injection of Egg Digest one horn of the uterus was removed and a Schultz-Dale test performed.

Schultz-Dale test.—Negative to Egg Digest, strongly positive to egg white (Fig. 2).

Five days later—

Treatment.—Intravenous injections of Egg Digest at ten-minute intervals:

Injection 1.—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Slight bristling

Fifteen minutes later—

Shock dose (2.5 M.L.D)—Bristling and twitching nose. One hour later, the animal was killed.

Schultz-Dale test.—Negative to egg white (Fig. 3).

Lung perfusion test.—Positive to egg white (Fig. 4).

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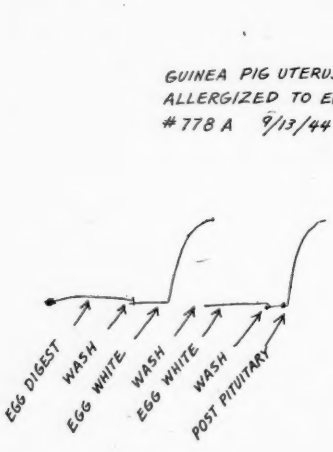
*Regarding the chemical composition of egg digest, see Table II of first paper of this series.[11]

jection of 0.1 c.c. of 50 per cent egg white in saline. After twenty-one days, these animals were so highly hypersensitive that an intravenous injection of 0.5 c.c. of a 0.1 per cent egg white solution led to instantaneous death accompanied by the most severe manifestations of anaphylactic



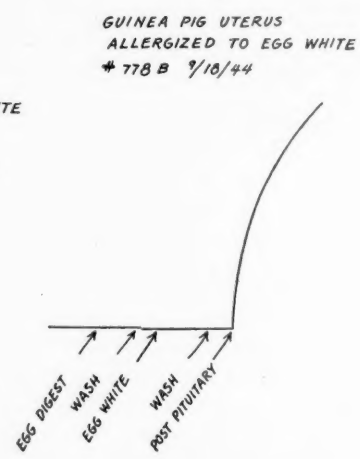


Fig. 2. *(left)* Schultz-Dale test performed upon the uterus of guinea pig No. 778 allergized to egg white and treated with intravenous skeptophylactic injections of egg digest. (Only one horn of the uterus was removed and the animal was subsequently used in the second part of Experiment 1, Fig. 3). There was no reaction upon the addition of egg digest. A violent reaction followed the addition of egg white, indicating the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white, proving that the preceding one was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

Fig. 3. *(right)* Schultz-Dale test performed upon the second uterine horn of guinea pig No. 778 allergized to egg white and treated with intravenous skeptophylactic injections of egg digest followed by intravenous injection of 2½ minimal shock dose of egg white (same animal as used in Figure 2). There was no reaction upon the addition of egg digest or egg white, indicating the absence of antibodies in the uterus. The posterior pituitary extract was added as a check upon the sensitivity of the uterus.

shock. Therefore, in this group of animals, the minimal lethal dose was 0.50 c.c. of a 0.1 per cent egg white solution.

Guinea pigs previously intraperitoneally allergized to egg white were given mounting doses of egg propeptan intravenously, and one uterine horn of an animal so prepared, removed two hours after the last injection, showed a negative reaction to the egg propeptan, but a positive reaction to the egg white (Fig. 2).

Five days later, when the abdominal wound had healed completely and the animal seemed healthy and was eating normally again, the same pretreatment schedule was repeated. This time, however, two and one-half times the minimal lethal dose was injected intravenously fifteen minutes

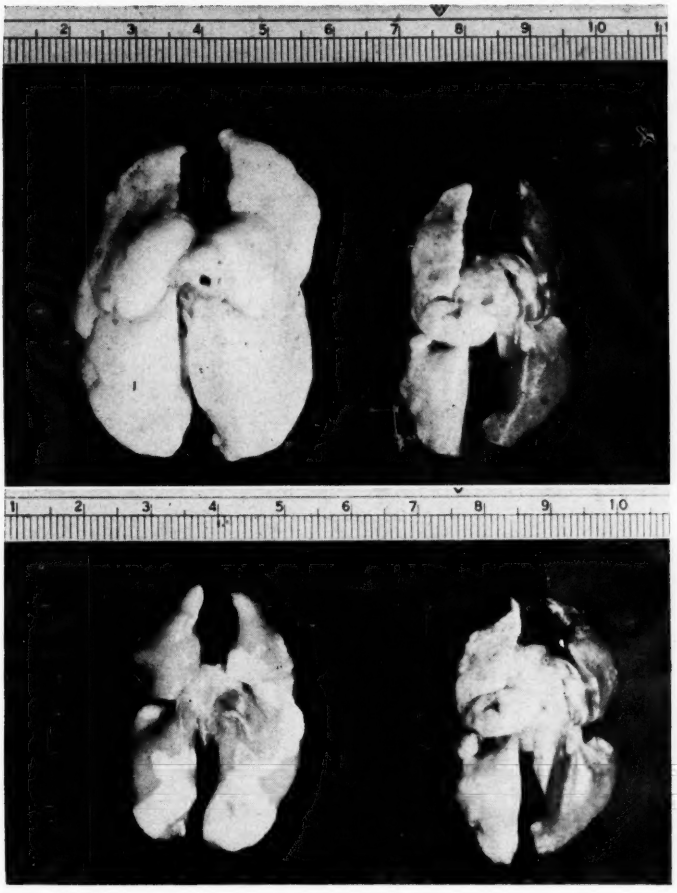


Fig. 4. Lung perfusion test performed upon the lung of guinea pig No. 778 allergized to egg white, treated with intravenous skeptophylactic injections of egg digest and killed *one hour* after surviving 2½ minimal lethal shock doses of egg white. The lung *(left)* reacted with marked inflation indicating the presence of considerable quantities of antibodies. A control lung of a nonallergized animal of the same weight *(right)* showed negative reaction in the lung perfusion test.

Fig. 5. Lung perfusion test performed upon the lung of guinea pig No. 793 allergized to egg white treated with intravenous skeptophylactic injections of egg digest and killed *six hours* after surviving 2½ minimal lethal shock doses of egg white. The lung *(left)* showed no inflation, indicating the absence of antibodies. A control lung of a nonallergized animal of the same weight *(right)* showed negative reaction in the lung perfusion test.

after the last injection, but the animal showed no allergic response whatsoever. When the animal was killed by a blow on the head an hour later, and the Schultz-Dale test was performed on the second uterine horn, there was no reaction to egg white (Fig. 3). Evidence that the uterus had not lost its reactivity was given by its strong response to posterior pituitary extract.

While the animal was clinically protected against two and one-half times the minimal lethal dose, and the uterus was found to be free from antibodies, the lung reacted to the lung perfusion test with marked inflation when flooded with egg white solution (Fig. 4). This shows that there was still an abundance of antibodies in the guinea pig's primary shock tissue (the lung is generally regarded to be the shock tissue in these animals). It is to be noted, however, that the animal was killed *one hour* after the injection of the shock dose. When the guinea pig is not killed until *six hours* after administration of the shock dose, the antibodies in the lung are found to be satiated, as shown by a negative lung perfusion test (Fig. 5). The antibodies in the uterus were found to be neutralized in some cases, at this time, while in other animals the presence of antibodies could again be demonstrated.

Experiment 2

Guinea pig No. 793 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

Treatment.—Five intravenous injections of Egg Digest at ten-minute intervals.

Injection 1.—Egg Digest representing 1.0 mgs. of Soluble Nitrogen—No reaction
Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4.—Egg Digest representing 10.0 mgs. of Solumble Nitrogen—Bristling
Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Bristling

Fifteen minutes later—

Shock dose (2.5 M.L.D.)—Bristling

Animal killed six hours later

Schultz-Dale test—Negative

Lung perfusion test—Negative (Fig. 5).

When the animal is not sacrificed until *twelve hours* after administration of two and one-half times the shock dose, both uterus and lung again show positive reactions to egg white. This indicates that the antibody-satiation was only temporary and that, in other words, the neutralization is overcompensated by the presence of newly formed antibodies in the shock organs.

The first part of Experiment 1 has already shown that the mere administration of mounting doses of propeptans, intravenously, does not afford any protective action whatsoever. The intravenous injection of the food digest must be followed by an injection of the given food protein to produce the phenomenon of (temporary) de-allergization, as evidenced by clinical insensitiveness to two and one-half times the minimal lethal dose and by the negative results of the Schultz-Dale test, and the lung perfusion test.

This de-allergization takes place in the uterus a short time (one hour) after administration of a multiple minimal lethal dose and continues some five or six hours. In the lung, however, de-allergization does not take place until six hours after the injection but is still demonstrable nine hours after the injection. The possible explanation may be that it requires more time to satiate all the antibodies in the lung because the lung is, of course, a considerably larger organ, and thus, contains a greater number of antibodies to begin with, and, also, because the lung is the primary shock organ in the guinea pig.

The reasons for the unreactivity on the part of the highly sensitized uterus and lung after pre-administration of type-specific propetans are not, as yet, fully understood. The senior author[12] has expressed the opinion that the action of the propeptans are based on the principle of skeptophylaxis (anti-anaphylaxis)—i.e., the concept that administration of food digest brings on micro-shocks which are strong enough to neutralize temporarily the available supply of antibodies. This results in what is known as a negative, or anergic, phase in which the newly administered antigen fails to encounter antibodies, and, therefore, cannot evoke an anaphylactic reaction. After twelve hours, however, this state of neutralization comes to an end, as shown by the positive Schultz-Dale test and lung perfusion test. Clinically, on the other hand, the animal is still protected against two and one-half times the minimal lethal dose.

Other immunologic conditions are achieved when the skeptophylactic treatment of the animals is carried out by intravenous administration of gradually mounting doses of minute quantities of the native (i.e. undigested) food protein, as shown in Experiment 3.

Experiment 3

Guinea pig No. 791 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

Treatment.—A series of increasing doses of egg white at ten-minute intervals (M.L.D.: 0.25 c.c of 0.1 per cent egg white solution).

Injection 1.—0.1 c.c. of 0.01% egg white—No reaction
Injection 2.—0.25 c.c. of 0.01% egg white—No reaction
Injection 3.—0.50 c.c. of 0.01% egg white—No reaction
Injection 4.—1.00 c.c. of 0.01% egg white—No reaction
Injection 5.—0.10 c.c. of 0.10% egg white—No reaction
Injection 6.—0.20 c.c. of 0.10% egg white—Bristling
Injection 7.—0.50 c.c. of 0.10% egg white—Bristling

Animal killed three hours after the last injection and a Schultz-Dale test and a lung perfusion test performed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

This skeptophylactic pre-treatment also succeeds in protecting a certain percentage of the animals against a double minimal lethal dose, but when the animals are sacrificed one, two, three, six, twelve hours later, the uterus and lung show strong reactions to egg protein (except for a few cases in which the lung perfusion test was negative six hours after this injection series). Thus, repeated injections of undigested protein cannot

produce even temporary de-allergization, immunologically, speaking. In this connection, it is important to note that these experiments must be performed most cautiously, with much smaller doses than when protein digests are used, for the danger of evoking a fatal anaphylactic shock in

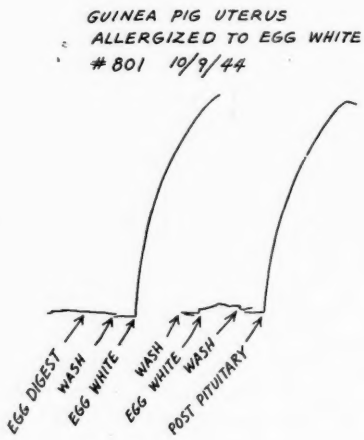


Fig. 6. Schultz-Dale test performed upon the uterus of a guinea pig No. 801 allergized to egg white and treated with intravenous injections of a series of increasing doses of egg white at two-day intervals (method of hyposensitization). The animal was killed *six hours* after the last injection. There was no reaction upon the addition of egg digest. A violent reaction followed the addition of egg white indicating the presence of considerable quantities of antibodies. No reaction followed a second addition of egg white, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

the guinea pig is far greater when native protein is injected. Yet the seventh injected dose (0.50 c.c. of 0.1 per cent egg white) contains only 0.01 mg. of soluble nitrogen, as compared with the 20 mg. of soluble nitrogen in the egg digest which can be given with impunity at the fifth injected dose. Apparently, even such minute quantities of native protein are too great to elicit micro-shocks, which alone are able to neutralize the antibodies. Thus, these experiments also demonstrate that the food protein digests are superior to the native food proteins, from the therapeutic viewpoint.

This becomes even more clearly apparent when the native food protein is injected in gradually mounting doses every twenty-four to forty-eight hours (method of hyposensitization), instead of intervals of ten or twenty minutes. In this manner, the animals can be protected against a quadruple minimal lethal dose. However, even after eight such injections, the Schultz-Dale test and the lung perfusion test are still strongly positive, showing that this method does not reduce the number of antibodies.

Experiment 4

Guinea pig No. 786 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

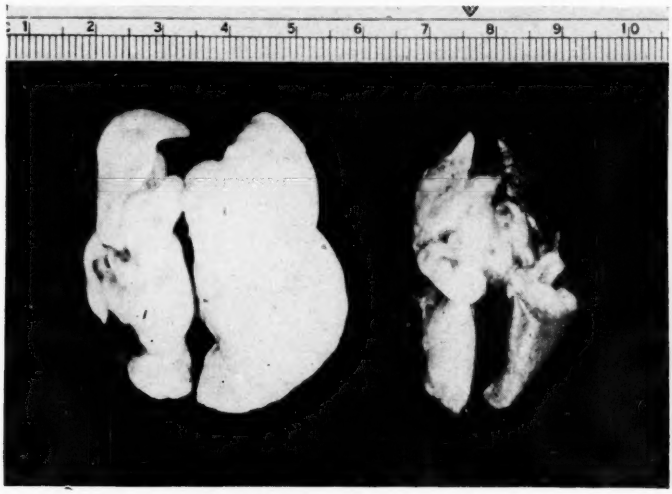


Fig. 7. Lung perfusion test performed upon the lung of guinea pig No. 801 allergized to egg white and treated with intravenous injections of a series of increasing doses of egg white at two-day intervals (method of hyposensitization). The animal was killed six hours after the last injection. The lung *(left)* showed marked inflation, indicating that the number of antibodies were not reduced. A control lung of the nonallergized animal of the same weight *(right)* showed a negative reaction in the lung perfusion test.

Treatment.—A series of daily increasing doses of egg white intravenously (1 M.L.D.—0.5 c.c. of 0.1 per cent egg white solution)

9/14/44—0.1 c.c. of 0.1% egg white—No reaction
9/15/44—0.2 c.c. of 0.1% egg white—No reaction
9/16/44—0.5 c.c. of 0.1% egg white—No reaction
9/17/44—0.5 c.c. of 0.1% egg white—No reaction
9/18/44—0.5 c.c. of 0.1% egg white—No reaction
9/19/44—1.0 c.c. of 0.1% egg white—No reaction
9/20/44—1.0 c.c. of 0.1% egg white—No reaction
9/21/44—0.2 c.c. of 1.0% egg white—No reaction

Animal killed three hours after the last injection.

Schultz-Dale test—Positive

Lung perfusion test—Positive

Experiment 5

Guinea pig No. 801 allergized to egg white.

Intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

Treatment.—A series of increasing doses of egg white administered intravenously at two-day intervals.

9/29/44—0.50 c.c. of 0.01% egg white—No reaction
10/ 1/44—0.10 c.c. of 0.10% egg white—No reaction
10/ 3/44—0.25 c.c. of 0.1 % egg white—Bristling
10/ 5/44—0.25 c.c. of 0.1 % egg white—No reaction
10/ 7/44—0.50 c.c. of 0.1 % egg white—Bristling
10/ 9/44—1.00 c.c. of 0.1 % egg white—No reaction

Animal killed six hours after the last injection.

Schultz-Dale test—Positive (Fig. 6)

Lung perfusion test—Positive (Fig. 7)

Hitherto, the discussion has been confined to conditions in animals that (1) had been allergized parenterally, (2) were given for protection the

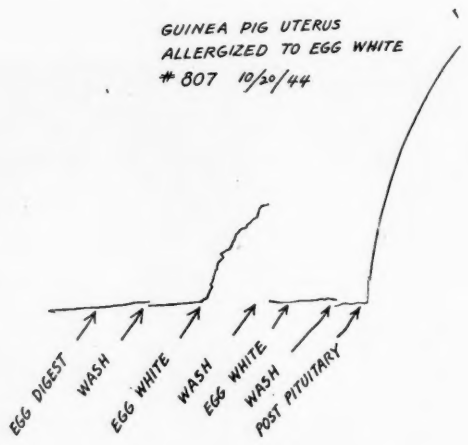


Fig. 8. Schultz-Dale test performed upon the uterus of a guinea pig No. 807 allergized to egg white, treated orally with egg digest followed by intravenous injections of multiple shock doses of egg white (three treatments). The animal was killed *six hours* after the last shock dose. There was no reaction upon the addition of egg digest. An attenuated positive reaction followed the addition of egg white, indicating partial neutralization of the antibodies. No reaction followed a second addition of egg white, proving that the preceding reaction was specific. A final addition of posterior pituitary extract was made as a check upon the sensitivity of the uterus.

food digest intravenously, and (3) received the shock dose of egg white intravenously.

We shall now consider some experiments in which the animals were allergized by the parenteral route, but in which either the protective food digest or the subsequent shock-dose of egg white was administered orally.

Experiment 6 shows what happened when treatment consisted in administering the food digest by mouth on three consecutive days—in contrast to the results shown in Example 1, where the digest was administered intravenously at ten-minute intervals. The reasons for setting an interval of some sixty-six hours between the first oral administration of the digest and the administration of the shock dose of native protein, and for giving the shock dose shortly after the digest on three consecutive days, will be discussed in some detail in our third[12] communication, which will deal exclusively with the immunologic conditions of orally administered propeptans. Here we merely shall state that propeptans, given orally, afford protection five times against minimal lethal doses and more. However, also this treatment brings about only partial neutralization of the antibodies,

as shown by the positive, although definitely weaker, reactions following the Schultz-Dale test and the lung perfusion test (Figs. 8 and 9).

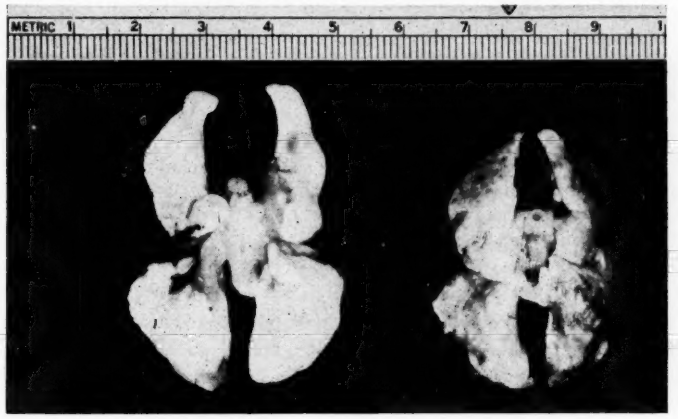


Fig. 9. Lung perfusion test performed upon the lung of a guinea pig No. 807 allergized to egg white treated orally with egg digest followed by intravenous injection of multiple shock doses of egg white (three treatments). The animal was killed *six hours* after the last shock dose. The lung *(left)* showed an attenuated reaction to egg white, indicating partial neutralization of the antibodies. A control lung of a nonallergized animal of the same weight *(right)* showed a negative reaction in the lung perfusion test.

Experiment 6

Guinea pig No. 807 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

Treatment.—(1) Oral treatment with Egg Digest (20 mgs. of Soluble Nitrogen) +0.2 grams of Glycyrrhiza +3.0 c.c. of water.

Sixty-six hours later—(2) Oral treatment with Egg Digest followed in one hour by 2.5 M.L.D. of egg white intravenously—Bristling

Twenty-four hours later—(3) Oral treatment with Egg Digest followed in one hour by (1) 2.5 M.L.D. of egg white intravenously—Bristling
(2) 5.0 M.L.D. of egg white intravenously—Bristling and gagging.

Twenty-four hours later—(4) Oral treatment with Digest followed in one hour by
(1) 2.5 M.L.D. of egg white intravenously—Bristling
(2) 5.0 M.L.D. of egg white intravenously—Bristling

Six hours after the last shock dose the animal was killed.

Schultz-Dale test—Attenuated positive (Fig. 8)

Lung perfusion test—Attenuated positive (Fig. 9)

But when the order is reversed—that is to say, when the digest is administered by intravenous injections and the shock dose of native protein is then given by mouth (Experiment 7)—the Schultz-Dale test is negative and the lung perfusion test gives an attenuated positive reaction corresponding to the conditions observed in Experiment 1.

Experiment 7

Guinea pig No. 757 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white.

Three weeks later the following treatment was instituted.

Treatment.—Intravenous injections of Egg Digest at ten-minute intervals.

Injection 1.—Egg Digest representing 1.0 mg of Soluble Nitrogen—No reaction
Injection 2.—Egg Digest representing 2.5 mgs. of Soluble Nitrogen—No reaction
Injection 3.—Egg Digest representing 5.0 mgs. of Soluble Nitrogen—No reaction
Injection 4.—Egg Digest representing 10.0 mgs. of Soluble Nitrogen—Slight bristling
Injection 5.—Egg Digest representing 20.0 mgs. of Soluble Nitrogen—Bristling

Thirty minutes after the last injection.

Shock-dose—By mouth 7.5 c.c. of egg white

Symptoms—Twitching of nose and gagging about ten minutes after the shock dose

Animal killed two hours after the shock dose

Schultz-Dale test—Negative

Lung perfusion test—Attenuated positive.

On the other hand, when the food digest is replaced by equal quantities of native protein, administered on seven consecutive days and then followed by the shock dose (either intravenously or by mouth), the animals are indeed protected, but there has been no antibody-neutralization, as shown by the fact that both the Schultz-Dale test and the lung perfusion test are strongly positive (Experiment 8). This conforms perfectly with the findings in Experiment 3.

Experiment 8

Guinea pig No. 818 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline. Three weeks later the following treatment was instituted.

Treatment.—Oral administration of egg white representing 20 mgs. of Soluble Nitrogen +0.2 grams of Glycyrrhiza, every day for seven days.

(Animal starved in empty cage overnight.)

1st Dose—11/ 7/44—No reaction
2nd Dose—11/ 8/44—No reaction
3rd Dose—11/ 8/44—No reaction
4th Dose—11/10/44—No reaction
5th Dose—11/11/44—No reaction
6th Dose—11/12/44—No reaction
7th Dose—11/13/44—No reaction

One hour after the seventh dose—

Oral administration of shock dose 7.5 c.c. of egg white +0.2 grams of Glycyrrhiza. No clinical symptoms noted.

Six hours later—

The animal was killed and a Schultz-Dale test and a lung perfusion test were performed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

Similar results are obtained when gradually increasing doses of native protein are administered by mouth on seven consecutive days (Experiment 9). This conforms with the findings in Experiment 4.

Experiments 2, 6 and 7 on the one hand and Experiments 3, 4, 8 and 9, on the other hand, show that there is a difference between the immunologic effects of food propeptans and of native protein, since the former bring about, at least, partial and temporary de-allergization as shown by the

negative or attenuated Schultz-Dale test and the lung perfusion test. Food propeptans induce micro-shocks, and thus lead, first, to partial and temporary, and, later, to complete but temporary de-allergization. Native protein, on the other hand, leads to an increase in the number of circulating antibodies, and thus to temporary hyposensitization.

Experiment 9

Guinea pig No. 819 allergized to egg white by intraperitoneal injection of 0.1 c.c. of 50 per cent egg white in saline.

Three weeks later the following treatment was instituted.

Treatment.—Oral administration of daily increasing doses of egg white +0.2 grams of Glycyrrhiza.

1st Dose—11/ 7/44—0.25 c.c. of egg whiite—No reaction
2nd Dose—11/ 8/44—0.50 c.c. of egg white—No reaction
3rd Dose—11/ 9/44—0.75 c.c. of egg white—No reaction
4th Dose—11/10/44—1.0 c.c. of egg white—No reaction
5th Dose—11/11/44—1.5 c.c. of egg w ite—No reaction
6th Dose—11/12/44—2.0 c.c. of egg white—No reaction
7th Dose—11/13/44—2.5 c.c.of egg white—No reaction

Six hours after the last dose the animal was killed.

Schultz-Dale test—Positive

Lung perfusion test—Positive

DISCUSSION

Food propeptans (i.e. food proteins digested enough to be free of native protein, but not to the point of losing their type specificity) do not, in themselves, afford protection. It is only when they are followed by administration of the given food allergen that they bring about a more or less lasting state in de-allergization, the duration depending on the manner in which the propeptans are administred (quantity, timing, route).

When an animal has been given intravenous injections of mounting doses of propeptans, followed by intravenous administration of multiple shock-doses, and the animal is killed one hour after treatment, the Schultz-Dale test method will reveal no antibodies in the uterus, but the lung perfusion method will disclose the presence of an abundance of antibodies in the lung. However, when the animal is sacrificed six hours after the shock dose, both uterus and lungs are free of antibodies (negative Schultz-Dale and lung perfusion tests). In other words, it takes about six hours for the antibodies in these two organs to be neutralized. The reason why it takes the antibodies of the lung longer than the antibodies of the uterus to be neutralized, can, in all probability, be found in the simple fact that the lung is by far the larger of the two organs and thus contains a greater number of antibodies, and, moreover, in the fact that the lung is the primary shock organ in the guinea pig. However, while neutralization of the antibodies is complete after six hours, it is only temporary: twelve hours after the administration of the shock dose, the Schultz-Dale test and the lung perfusion test are again positive.

On the other hand, when the skeptophylactic treatment is administered by intravenous injections of gradually mounting doses of minute quantities of the native (i.e. undigested) food protein, clinical protection is also

achieved, but no neutralization of antibodies can be demonstrated (both Schultz-Dale and lung perfusion tests positive). Thus, even these minute quantities of native protein are apparently too great to elicit micro-shocks which alone are able to neutralize (satiate) the antibodies. These experiments demonstrate, therefore, that from the immunologic, as well as, from the therapeutic viewpoint, the food digests (propeptans) are superior to the native proteins.

The immunologic action of the food propeptans may be explained in the following manner: they engender micro-shocks which, in turn, lead to specific skeptophylaxis (anti-anaphylaxis of Besredka[1]). These propeptans bring about, first, partial and transient, then complete but transient, and, ultimately, complete and lasting neutralization (satiation) of the tissue antibodies. To this immunological state the term "de-allergization" is applied by the senior author.[7]

SUMMARY

Exhaustive animal experimentation with food digests (food propeptans) show that food propeptans, given enterally or parenterally under appropriate conditions as to quantity and time, can protect guinea pigs against otherwise certain anaphylactic death.

The immunologic principles on which the protective action of food propeptans are based were studied experimentally and are discussed in some detail. As has been previously shown by the senior author there are two basic approaches by which to achieve clinical protection against anaphylaxis, namely, de-allergization and hyposensitization. Further experimental proof is presented.

Food propeptans operate by inducing micro-shocks causing first partial and temporary, later complete and lasting, satiation of the antibodies, thus, leading to de-allergization. On the other hand, native protein administered every day or every second day in the same or graduated doses increase the circulating antibodies leading only to temporary hyposensitization.

The results of these investigations seem to constitute experimental confirmation of the therapeutic value of specific propeptan therapy in food allergy in man.

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(Continued on Page 240)

COMBINED HELIUM AND EPINEPHRINE THERAPY

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THE use of helium and oxygen mixtures for the relief of asthma was originally suggested by Barach[2] in 1935. Epinephrine 1-100 by inhalation was suggested by Graeser and Rowe[4] in the same year. Epinephrine by inhalation had been used previously by Camps[3] in England but never in the very effective strength of 1-100. Both of these methods for the symptomatic relief of asthma have met with widespread acceptance and their usefulness is indeed very great.

The combination of the two in an easily utilized and if need be portable unit presents a method of quick and effective relief for most acute paroxysms of short duration and moderate intensity.

APPARATUS

Large cylinders of oxygen and helium (size C) are used in the hospital or the office. To these are attached the usual step-down gauges which indicate the volume of gas remaining in the tank as well as the liter flow per minute. High-pressure rubber tubing carries the gas to a stand which holds the face mask, rebreathing unit and circle filter, as well as several flowmeters which measure the flow of oxygen and helium in cubic centimeters and liters per minute (Fig. 1). The epinephrine vaporizing unit is intimately attached to the face mask (Fig. 2). This has several advantages. The patient is required to do nothing but breathe deeply. There is no change necessary in the shift from helium and oxygen to the epinephrine vapor and back again if need be. The vaporizing unit used is the DeVilbiss No. 40 which in general use has been found to be very effective and which because of its large transverse diameter of outlet allows a large amount of vapor to come forth. This unit can easily be removed from the machine for cleaning and the addition or replacement of fresh mixtures of epinephrine 1-100. It can be cut off from the machine by means of a sliding diaphragm (Fig. 2). This allows the unit to be used for the helium and oxygen. It is hoped that some future design might make the use of helium and oxygen mixture and the epinephrine simultaneous. The epinephrine used is of the glycerinated variety using Lockey's formula.[5] As pointed out by Suszman[6] and by Abramson[1] this is the most readily vaporized and gives the finest droplet formation and hence best permeation of the bronchial tree.

There are three flow meters. One measures the amount of helium, the second the amount of oxygen to the helium-oxygen bag, and the third uses oxygen or compressed air to vaporize the epinephrine 1-100.

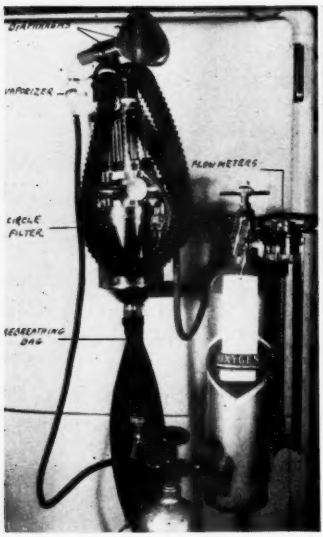

Fig. 1. Illustration of the component parts of the apparatus.

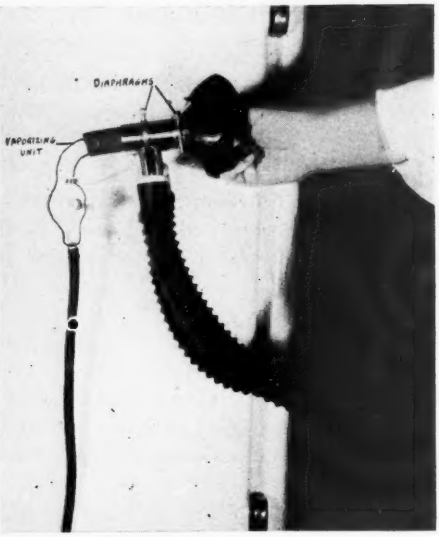

Fig. 2. Relationship of the mask to the vaporizing unit.

METHOD OF ADMINISTRATION

The patient is seated in a comfortable chair. If he is very apprehensive of the apparatus—and very few are, even the youngest of children have accepted it—he is allowed to hold the face mask instead of fastening it to him by elastic rubber bands (Fig. 3). A reasonable type of approximation should be made to avoid the escape of gases. The patient is then asked to breathe deeply while the epinephrine vapor is administered. Long deep inhalations are preferable to short shallow ones. After approximately thirty seconds—six to ten breaths—the vapor is discontinued and the helium-oxygen mixture administered by shifting the diaphragms on the face mask. Once the helium-oxygen mixture is established it is only necessary to add a small amount of oxygen as it is used up by the patient. This provides a definite economy, since helium is an expensive gas. The patient is allowed to breathe the mixture for about ten minutes, and frequently a return to the epinephrine vapor for three or four breaths is advisable.

More often the relaxation occurs within the first few minutes of treatment. At the termination there is often a coughing spell with variable amounts of sputum—sometimes unbelievable amounts. The pink color of the sputum is due to the oxidized medication. Occasionally the quantities of sputum are out of proportion to the physical findings of the chest and the clinical severity of the asthma. There are innu-

merable variations as to the amount of epinephrine vapor and helium and oxygen that may be inhaled. One should be guided by the clinical requirements of the case.

Fig. 3. The mask in place, showing the approximation by means of an elastic head support.

DISCUSSION

An inexperienced person can be trained to operate the apparatus satisfactorily. There is no danger of asphyxia with helium if oxygen is always used first in filling the bag and the helium added afterward. If one is particularly concerned with this point the 80 per cent helium-20 per cent oxygen mixture can be used instead of pure helium.

It is noteworthy that where organic obstruction is present, or where the mucous plugs are specially inspissated, the relief will be only partial, or completely absent. It is frequently desirable to administer iodides prior to treatment, particularly when the first treatment has been unsatisfactory. When no relief or slight relief is obtained, the diagnosis of allergic asthma should come under scrutiny to rule out the possibility of obstruction by neoplasm, enlarged bronchial nodes, foreign body, et cetera. In those cases, x-ray and bronchoscopy should be used.

The usual cautions and contraindications in the use of epinephrine 1-100 should be borne in mind. The use of helium and oxygen alone gives some relief for the duration of its application only, and from the standpoint of the ambulatory patient is not worth while. Helium and oxygen

for the cyanotic patient, of course, is still indicated, but such a case should be hospitalized.

Significant in the use of the apparatus is the low cost of operation. Smaller portable units, using size D cylinders, can be used, but unless portability is of prime importance, it is not desirable because of the expense.

In order to better indicate the types of cases most benefited, the following classification is suggested:

1. *Complete loss of pulmonary reserve*—dyspnea at rest.

A. Temporary—less than seventy-two hours and due to bronchospasm with or without edema and mucus which is not inspissated. These cases are greatly aided by combined therapy.

B. Those of longer than seventy-two hours—usually with inspissated mucus. These cases are not effectively relieved for anything but a very short time. However, if iodides are given in full therapeutic doses and then followed by this combined therapy, a pulmonary cleansing with very beneficial result is often effected. These cases may have to be bronchoscoped.

2. *Partial loss of pulmonary reserve*—no dyspnea at complete rest, but evoked with effort.

A. Evoked with mild effort.

B. Evoked with moderate to marked effort.

These cases are benefited in inverse proportion to the amount of bronchial mucus and edema present.

3. *No loss of pulmonary reserve.* These cases are in the interparoxysm stage and hence need only basic allergic care without any symptomatic treatment. It is understood that the above classification makes the assumption of a normal cardiac function and a lack of irreversible pulmonary pathology such as emphysema, bronchiectasis, pulmonary fibrosis, et cetera. The effect of the combined therapy can be demonstrated within fifteen to twenty minutes after the conclusion of treatment by the determination of the vital capacity.

It has been found that the use of the apparatus will relieve an acute paroxysm in the office with practically no blocking effect on skin-testing procedures.

It is noteworthy that this apparatus can be used to vaporize any vaporizable material and therefore other combinations of therapy requiring the mixture of gases and vapors can utilize this apparatus. (The use of penicillin in this apparatus is a possibility.)

CONCLUSIONS

1. A method of combining the use of epinephrine 1-100 and helium and oxygen in one apparatus is presented.

2. The use of expensive gases is kept down to a minimum by rebreathing, using the circle filter.

3. An effective method of speedy bronchial relaxation with minimal side effect for ambulatory patients is presented.

(Continued on Page 206)

THE DIAGNOSTIC VALUE OF THE EOSINOPHILE IN ALLERGIC STATES

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HISTAMINE release and the relation of eosinophiles to the allergic reaction still remain controversial. Code[1,2] first used the normal rabbit to determine the relative proportion of the histamine content of the cells compared with the plasma. His findings were quite consistent in that the "white cell layer" between the plasma and red cells in the contrifuged specimen of normal whole blood contained almost "ninety per cent of the histamine content of the whole blood when compared to the plasma and red cells." Other observations by Code on the changes of the histamine content in various animals, particularly the guinea pig and the dog, during anaphylactic shock, showed that the histamine values rose three to nine times in the shocked animals, the escape of histamine taking place in the white cell layer, chiefly from the eosinophiles. Code[3] concluded that histamine released during the anaphylactic shock was an important factor in producing the symptoms and pathologic changes in the reaction. There is no doubt that histamine plays a very important part, whether primary or incidental, coincident with the damaged sensitized cell in anaphylaxis and allergy. Code and Macdonald[4] reported cases of eosinophilia in which the histamine content of the blood was above the normal. Rose[14] also has reported cases of eosinophilia with an increased histamine level in the blood. In other cases of eosinophilia, the blood histamine was definitely below normal. The observations of Randolph and Rackemann[13] showed that five of eight cases with bronchial asthma had eosinophile counts which were comparatively higher than those recorded by Code and Macdonald but the blood histamine level was normal. These observations should justify the consideration of the eosinophile response as a very important primary factor in the allergic mechanism. Clinical observations of the eosinophile in allergic states, therefore, seem justified. These observations, although elementary, are based upon our experience in studying nasal secretions and blood smears for the presence of eosinophilia.

Our observations have extended over a period of several years and comprise the evaluation of more than five thousand smears of the nasal secretions and the blood.* This report represents an effort to stimulate the use of these valuable procedures, which Hansel[6] has so well established. Based upon the information thus obtained, we believe that a cytologic examination of the blood or nasal secretion ranks second to a careful history[16] and should precede the other diagnostic procedures, such as skin tests, et cetera. A nasal examination may be misleading and inconclusive if it is not preceded by a thorough, intelligent history with ref-

*The major portion of this work comes from the St. Francis Hospital Allergy Clinic with the technical assistance of Miss Mary Walter.

erence to allergy, and followed by proper study of the nasal secretion. Other observers in widely separated areas have also recorded the fallacy of relying upon local nasal examination alone. In the Pittsburgh area smog, smoke and irritating chemical particles may cause a very red nasal mucous membrane in allergic patients. The following three cases corroborate the foregoing statements:

Case 1: D. M., aged eleven, reported to the Nose and Throat Clinic in September, 1940, on account of enlarged tonsils and for consideration of a tonsillectomy. The history of allergy was recognized; an allergic survey and control were instituted. The nasal smear showed many eosinophiles and they were also increased in the blood. She is much improved now. Tonsillectomy may be performed later if the indications justify it. It should not be instituted with the idea of controlling the allergic symptoms.

Case 2: W. H., aged four, reported to the Clinic with a history of "always being in the hospital" on account of "severe colds" and convulsions. After an allergic survey, including a nasal smear which revealed no eosinophiles but many organisms, bacterial vaccine was given with excellent results. This boy has been followed for four years, during which time he has had three slight respiratory infections. Recently the first convulsion, since bacterial immunization was started, was noted during an attack of scarlet fever. On the basis of these observations common cold vaccines should not be administered before the allergic state is known and the presence of many organisms is demonstrated in the nasal secretion.

Case 3: E. S., aged eleven, gave a history of "severe sinus trouble." Several nose and throat operations gave no relief; in fact, probably made him worse. Eosinophiles were noted in the nasal secretion. They were moderately increased in the blood. Allergic management has resulted in marked improvement. Had it been instituted earlier many operations may have been avoided. This patient has been observed for three years. He has gained 25 pounds and has been almost free of nasal symptoms until last winter. Some of his nasal symptoms returned after he ate some foods to which he was clinically sensitive.

These case reports were presented to emphasize the value of nasal smear studies in differentiating allergy from infection in children. From the symptomatic standpoint allergy may simulate acute or chronic infection.[12] Correct diagnosis may be established only by repeated study of the nasal secretions. Hansel[8] has emphasized the value of the allergic investigation before recommending nose and throat operations. During the past few years better co-operation among the pediatrician, the otolaryngologist and the allergist has developed. By this co-operation unnecessary tonsillectomies may be avoided.

Is the eosinophile related to the immunologic response? For many years it has been recognized that eosinophilia will fluctuate with immunologic reactions. It is particularly significant in nasal allergy that when the pH of the nasal secretion falls low or toward the acid side there is a complete disappearance of the eosinophiles. When the pH returns to the alkaline side there is a return of the eosinophiles. Kaufman[10] states that "The relationship between eosinophilia and allergic disease is not clear."

EOSINOPHILE STUDIES ON 100 CONSECUTIVE PATIENTS VISITING THE ALLERGY CLINIC

Number of Patients		100
Number of Nasal Smears		60
Eosinophiles only	7	
Eosinophiles and neutrophiles	6	
Eosinophiles and organisms	9	
Eosinophiles, neutrophiles and organisms	27	
	49	
Neutrophiles only	3	
Organisms only	4	
Neutrophiles and organisms	3	
	11	
Number of Blood Smears		39
Eosinophilia over 5 per cent		18

Three primary sources of the eosinophile have been considered: (1) the local shock tissue, (2) the blood, and (3) the bone marrow or other blood-cell forming organs.

Some observers believe that eosinophiles may be formed in the local tissues. Salaris and Guarnari[15] reported the following ingenious experiment:

Fifteen patients suffering from bronchial asthma or allergic rhinitis were tested intracutaneously with specific allergens. Blood was drawn from the finger tip at five, twenty, forty and sixty minutes, respectively, after the onset of the positive cutaneous reaction and the percentage of eosinophiles was determined. An increase in eosinophiles was noted within five to twenty minutes. This increase was more pronounced in the blood taken from the arm on which the cutaneous testing was performed. This finding according to the authors is suggestive of the local origin of eosinophiles. Their findings could not be duplicated in an extremely sensitive individual.

Patient C. R., aged twenty-two, was admitted to the hospital, December, 1942, in severe shock, unconscious, and with compound fractures of both legs. No tetanus antitoxin was given because the history suggested a severe sensitivity to horse serum. The allergic symptoms were asthma, urticaria, rhinitis and gastro-intestinal upsets to certain foods. An allergic survey was done several weeks later during the convalescence.

Intradermal Skin Tests

Positive tests were obtained to many foods and inhalants.

Dust (1-10) +++	Mustard ++++
Grass (1,000 PNU/cc) +++	Peanut ++++

Tests for mustard and peanut were performed at one sitting. A constitutional reaction resulted.

Horse Serum	*Horse Dander*
1-1,000,000 +	1-4,000,000 0
1-100,000 +++	1-400,000 +++
1-1000 ++++	1-40,000 ++++

At the time of a skin test to horse dander, 1-40,000 dilution the blood showed three per cent eosinophilia. Fourteen minutes later there was a two per cent eosinophilia and the horse dander reaction was four plus.

Occasionally it is necessary to study the eosinophile content of other tissues or body secretions, depending upon the nature and location of the allergy. Eosinophiles may occur in large numbers in the stools of patients suffering from gastro-intestinal allergy, in the urine in urinary system allergy, in sections of nasal polyps or in the appendix and other pathologic tissues. Antral washings may be quite revealing. Operations on the nose of patients with nasal allergy may be instrumental in aggravating the allergic symptoms. Dutton[5] suggests that frequently allergic reactions precede the infection of appendicitis just as there are seen infections super-imposed on allergic asthma. He based his conclusions upon a detailed study of the eosinophiles noted in the pathologic sections from one hundred and twenty-three appendices removed in cases of appendicitis.

An increased eosinophilia may occur in other disease processes such as in parasitic infestations; consequently, one should be cautious in considering an eosinophilia to be allergic in origin in the presence of any other disease associated with this phenomenon. Pulmonary eosinophilic infiltration or "Loeffler's syndrome" is considered by many as an allergic reaction. Communications from military observers from many parts of the world point out that eosinophilia is noted in many diseases occurring in the tropics other than those suspected previously. Some of these observers believe that occasionally the eosinophilia is similar to that found in "Loeffler's syndrome." Familial eosinophilia has also been reported on several occasions. Our observations would indicate that the presence of five per cent eosinophiles in the blood, or above, is an increase. In our patients the eosinophilia varied from five to twenty per cent and on rare occasions it was increased to as high as 35 per cent. An eosinophilia without a demonstrable allergic cause was not observed more than three to four times.

METHODS OF OBTAINING NASAL SMEARS

1. Have the patient blow his nose upon wax paper or cleansing tissue.
2. Swab-stimulation is used when the nasal mucosa is fairly dry. This method has not been very satisfactory. It is time-consuming and as a rule only watery secretion and epithelial cells are obtained.
3. The material may be obtained by having the patient "hawk" in instances in which a post-nasal discharge is present.

The first method is preferred as a majority of patients usually have considerable nasal discharge. If secretion is not available at the time of

the examination, the patient is given a packet consisting of two clean slides, toothpicks and waxed paper. He is instructed to make two slides at different times and to bring them to the Clinic or office at the next visit. If the patient is well instructed this method is very successful.

When changes occur in the symptomatology a smear should be examined. It is often necessary to determine whether or not a common cold is present. Hansel[7] emphasizes the importance of following these changing conditions by repeated examination. Occasionally it may be noted that there is a difference in the cytologic picture in specimens taken from each side of the nose.

PREPARATION OF THE SLIDES AND STAINING

Giemsa, Wright's Eosin-methylene blue, or Hansel's stain may be used. Recently Hansel has supplied us with his latest polychrome stain. The staining is accomplished with one solution. It stains bacteria also. This new stain has given excellent results. The value of cytological studies of nasal secretions cannot be overemphasized to the student. He should be taught that nasal smear examination is as simple as differential blood counting and frequently almost as important.

The simple staining method using Wright's is as follows:

The secretion is spread thin on the slide and allowed to dry in clean air. After it is completely dried, the Wright's stain is applied and then the distilled water. Wash with distilled water. As a general rule the staining times are one-half that for blood smears. Stand the slide on end or dry over a small electric bulb. Do not blot.

Hansel's[9] technique for nasal and bronchial secretions with his new stain is as follows:

1. Collect secretion by having patient blow nose on waxed paper.
2. Transfer secretion to slide—tease out with toothpick so as to avoid thick masses. Make two or three smears if there is enough material.
3. Dry smears in air or gently over a flame.
4. Mark across slide next to label with paraffin stick to prevent overflow.
5. Cover completely with stain and allow to stand thirty to forty-five seconds, giving the longer period to thick or sticky smears.
6. Add distilled water to take up stain as in Wright's technique and allow to stand about thirty seconds. For best results neutralize the distilled water by adding one drop of one per cent potassium carbonate to each 30 c.c.
7. Pour off stain and flood slide with distilled water to remove excess stain.
8. Flood slide with 95 per cent ethyl alcohol. Drain off and dry slide over a flame.
9. If the blue color is too intense, flood slide with ninety-five per cent

ethyl alcohol to which one drop of one per cent hydrochloric acid has been added to 30 c.c. The amount of blue color removed depends upon the length of time the acid-alcohol is allowed to remain on the slide.

10. Pour off acid-alcohol and then flood with plain 95 per cent ethyl alcohol again.

11. Always examine the stained smear under the microscope before using the acid-alcohol solution. The acid treatment intensifies the red in the eosinophile by removing overlying blue. Too much acid may take the blue out of the neutrophiles and give them a pink color. If the neutrophiles are pink upon the first examination, stain another specimen and allow about fifteen to twenty seconds longer for the stain to act before adding the water.

12. In the examination of smears, the magnification must be 125 to 150. Using a 10 x objective, the eye piece, therefore, should be 12.5 or 15 x. Use a moderately strong clear light.

All the slides should also be examined with the oil emersion lens; this is essential to bring out the cellular details and to recognize bacteria. It greatly limits the size of the field, however, and more time is required for examination. A cover slip should not be used.

The characteristics of the eosinophile are as follows:

1. It is larger than the neutrophile.
2. The cellular membrane is fragile and many broken cells with loosely scattered eosinophilic granules may be observed.
3. The nuclei are usually two in number and stain blue.
4. The cytoplasm is filled with large acidophilic granules which stain brilliantly orange-red.

No cell should be designated as an eosinophile unless it conforms to this description.

Although preliminary experiments have been inconclusive, some observers have presented sufficient evidence to suggest that the production of eosinophiles is in some manner related to the release of histamine. Code[1] has shown that the principal source of histamine in the blood stream is probably the circulating eosinophiles. To explore this premise a patient with exfoliative dermatitis was given intravenously the salt equivalent of one mgm. of histamine. At the time of the injection the eosinophile count was three per cent and twelve hours later it was 5 per cent. This was not a significant rise. A higher count might have been incurred earlier. Moon, Lieber and Kennedy[11] showed that in normal individuals after the intravenous histamine, leukocytosis took place in three to five hours.

The cytoplasm[4] of the polymorphonuclear cells of the dog is almost devoid of stained material and relatively few eosinophiles are present. In contrast to this the polymorphonuclear cells of rabbit blood contain eosino-

phile granules. This is the normal appearance of rabbit blood and the cells have been referred to by hematologists as pseudo-eosinophiles. These observations in animals might suggest that reversible chemical compounds in the cytoplasm of the polymorphonuclear cell determine the size and staining qualities of the granules.

INTERPRETATION

The clinical observer should evaluate the significance of the smears at the time of the examination of the patient. An allergy laboratory in the clinic to facilitate handling of the slides is a distinct advantage.

In the cytologic examination all the elements in the smear should be observed and recorded. The organisms can easily be identified for they stain blue or purplish with the stains mentioned previously. The type of organism can often be identified. When the slide shows many organisms, a bacteriologic study of the secretion is indicated.

The eosinophiles may be very unevenly distributed or they may be conglomerated in a clump of mucus. One clump in the entire specimen may show hundreds of eosinophiles. An occasional eosinophile, especially in children, may be regarded as normal. A few neutrophiles are normally observed.

The presence of epithelial cells does not signify anything pathological. In a case of a sarcoma of the maxillary antrum, however, many sarcomatous cells were noted in the nasal smear. The diagnosis could have been made without the smear but it furnished substantiating proof.

MAJOR TYPES OF RESPONSES

1. *Allergy*

   E ++++ N 0 Or 0 Ep + —

2. *Infections*

   E O N +++ Or +++ Ep +

3. *Bacterial Allergy or a Secondary Infection on Top of An Allergic Response*

   E ++ N +++ Or +++ Ep +

E—Eosinophiles Or—Organisms

N—Neutrophiles Ep—Epithelial Cells

These three general classifications should be employed in the diagnosis of rhinitis and sinusitis.

Vasomotor rhinitis of the endocrine-sympathetic nervous system type usually has a profuse watery secretion with almost no cellular content.

The secretion in cerebrospinal rhinorrhea has the characteristics of spinal fluid.

Although eosinophiles may be present in large numbers in the nasal secretion, with the development of an acute coryza, they rapidly disappear.

The following case illustrates this point:

The patient, M. C., aged 28 years, was seen at the Clinic, December 19, 1940. She stated that "hives" appeared one-half hour after breakfast Wednesday, December

19, 1940. They had extended over the entire body but were relieved by an injection of epinephrine. She thought a "cold" was developing for a period of two to three days. Her nose was running and she was sneezing. A thyroidectomy had been performed on her several years ago but the last basal metabolic rate was minus ten. Her menstrual periods were regular and the last one was finished four days ago. There was no allergic history. Food taken the day before consisted of:

eggs*	coffee*	sugar	salmon	vanilla	cheese*
wheat*	milk*	apple*	chocolate	molasses	potato

*denotes the foods that were taken in large quantities but these were negative on intradermal testing.

December 29, 1940—The urticaria continued. The basal metabolic rate was minus eight and the temperature 98.6° F.

December 21, 1940—A nasal smear showed:

E ++++ N + — Or 0 Ep 0

Late in the afternoon of December 21, the nasal secretion increased and the next day the patient had a definite respiratory infection. Coincidentally, the urticaria disappeared.

December 25, 1940—A nasal smear showed:

E O N+ Or ++++ Ep +

Hansel states:

"In evaluating the number of neutrophiles in the secretion one must take into consideration that the neutrophilic response is always greater than the eosinophilic response and that the number of neutrophiles usually out-numbers the eosinophiles about ten to one, therefore, a plus-minus or a plus one of neutrophiles represents about ten times as many eosinophiles. In a smear with four plus neutrophiles the field is completely covered with them."

CONCLUSIONS

1. With a presentation of case histories, clinical and laboratory observations, the diagnostic value of the eosinophile in allergic states has again been emphasized.
2. A more general diagnostic use of this procedure should be employed. Besides the eosinophilia in the nasal secretions and in the blood, other more obscure symptoms may be established as of allergic origin by the recognition of this cell in the tissues involved.
3. Simple methods of collecting, staining and studying nasal smears have been presented.
4. All the elements in the nasal smear should be observed and recorded.
5. The controversial relationships between histamine release and eosinophilia have been discussed. Valuable information may be obtained by further observations on these phenomena.

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A Study of Oils Used for Intra-Muscular Injections. Brown, Willis E., Wilder, Violet M., Schwarts, Pauline: J. Lab. & Clin. Med., 29:259, 1944.

The ideal oil for intramuscular use should meet chemical requirements of stability and neutrality; it should be inert and nonirritating biologically; and physically it should be a good solvent or dispersing medium. Four oils (corn, cottonseed, sesame and peanut) were studied by the authors. Antigenic properties were studied by injecting patients at weekly intervals with two injections of each oil. These patients were tested two months later by patch and intracutaneous tests. Reactions were uncommon, but sesame and corn oil were considered less antigenic than the other two.

Biological reactions were tested on rats and rabbits. Within 24 hours there was an increase in round cells locally and the oil was diffused through the muscles. In two to three days sections were made and the oil was found to have accumulated in small droplets surrounded by a layer of fibrin. Peripheral to this layer were leukocytes and wandering cells.

Corn and sesame oil produced the least reaction as judged by the degree of fibrin and cell infiltration. Peanut oil produced the most marked reaction.

The Use of Histaminase in Prophylactic Tetanus Antitoxin Reaction. Eger, S. A., and Stone, J. E.: Penn. M. J., 47:371, 1944.

The authors studied a total number of thirty-one cases that developed serum reactions following the prophylactic administration of 1,500 units ATS. Fifteen of these were treated exclusively by the oral administration of twenty units of histaminase every three hours until symptom free. The untreated sixteen cases served as a control. The average period of recovery was apparently the same in both treated and control cases and there was no diminution of the intensity of symptoms in the histaminase-treated group.

HISTAMINIC CEPHALALGIA WITH DUODENAL ULCER

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EVEN though histamine was first isolated from ergot almost thirty-five years ago by Bayer and Dale, it has been only comparatively recently that effective clinical applications of the drug have been reported. Histamine, widely distributed in plant and animal tissues, is probably the most powerful dilator of capillaries known. It acts on nearly every organ of the body and alters the permeability of vessel walls allowing the escape of plasma proteins into extra-cellular fluid spaces. So far, the clinical uses of histamine have not yet measured up to its probable potential and ultimate usefulness.

The use of histamine in determining gastric secretory function has been well established and it has been reported to be of value in the treatment of physical allergy, urticaria, Ménière's Disease, histaminic cephalalgia, and multiple sclerosis. In a twelve-month period fifty cases of headache were studied by one of us (R.I.A.) of which four were typical of histaminic cephalalgia as first described by Dr. Bayard Horton. One case of histaminic cephalalgia presented an unusual complicating feature and we felt this case should be reported in order to add confirmatory evidence to Horton's previous studies.

This patient is a thirty-one-year-old man, with a previous history of typhoid fever, whooping cough, mumps, and measles. He had otherwise always been in good health, with no operations or injuries. The family history is irrelevant with no record of stomach trouble or allergy.

About fifteen years ago, he first noticed sharp, needlelike pain, localized to the region of the right eye. This pain lasted about an hour and came at any time of the day or night. The right eye watered, became markedly injected and the right nostril became obstructed. The pain was so severe that he was unable to remain quiet and he felt like striking his head against the wall. During this fifteen-year period he had had free intervals as long as three months, and then again he suffered from as many as three headaches in twenty-four hours. He had been treated for sinusitis.

About twelve years ago, which was three years after the onset of headaches, he noticed attacks of gnawing pain in the epigastrium for the first time. The pain came on one and a half to two hours after eating and often during the night. He vomited occasionally with relief from pain. On a number of occasions he vomited coffee-ground material and several times had vomited a cup or more of bright red blood. Tarry stools had been observed on a few occasions. The epigastric pain was relieved by soda and food. Hospitalization on an ulcer diet usually brought relief of gastro-intestinal symptoms in about two weeks. The digestive symptoms had tended to become progressively more severe and the last attack of ulcer distress continued for about five months.

Gastroscopic examination was normal. Proctoscopic examination was normal. The urinalysis and blood counts were within normal limits. The Kahn test was negative. No parasites, ova, typhoid or dysentery bacilli were found in the stools.

From the Gardiner General Hospital, Chicago, Illinois.

Roentgenoscopic and roentgenographic examination showed a normal esophagus and stomach. There was a marked deformity of the duodenal cap, just beyond the pylorus, and a shadow suggestive of a small crater was seen in this area. The above findings were well shown in the roentgenograms. These findings were reported as compatible with those of an ulcer of the first portion of the duodenum.

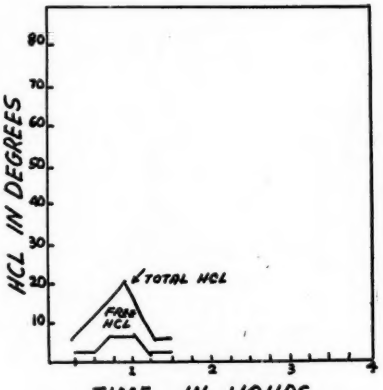


FIG. 1

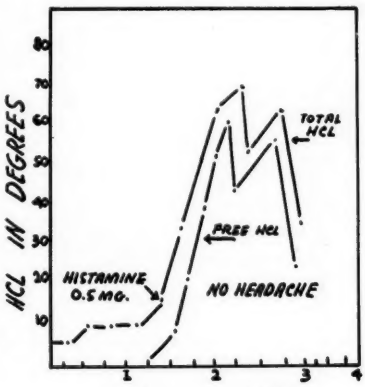
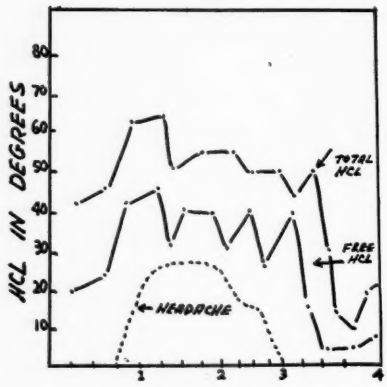


FIG. 2

Horton reported ten cases of histaminic cephalalgia complicated by acute duodenal ulcers with demonstrable crater formation. It was demonstrated in these cases that there was a rise in gastric acidity at the time of the headache, comparable to the rise in gastric acidity produced by an injection of histamine. It was presumed that these cases presented duodenal ulcers related to the rise in gastric acidity occurring during the attacks of histaminic cephalalgia. With these observations in mind, a study was made of the relationship between histaminic cephalalgia and the duodenal ulcer in our case. The histaminic celphalalgia in our case began approximately three years prior to the development of the symptoms suggesting peptic ulcer. Furthermore, it was noted that the attacks of ulcer distress were intermittent in occurrence and coincided with the attack of histaminic cephalalgia. A study of gastric acidity following a test meal of broth revealed very low values for total and free hydrochloric acid (Fig. 1) which is an unusual finding in active peptic ulcer patients.

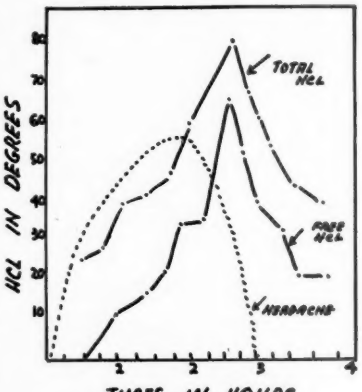
Histamine phosphate in a dose of 0.5 mg. used as a stimulant of gastric secretion showed a good response (Fig. 2) without production of headache. Curves of the values of total and free hydrochloric acid during typical attacks of spotaneous histaminic cephalalgia were obtained on numerous occasions. It will be noted that on one occasion while attempting to establish a base line for gastric acidity, a spontaneous attack of hista-

minic cephalalgia occurred (Fig. 3). There was a rise in free and total hydrochloric acid, that paralleled the onset, severity and cessation of the histaminic cephalalgia. Another gastric analysis curve is shown with the severity of the headache plotted simultaneously (Fig. 4). The gastric



TIME IN HOURS
SPONTANEOUS ATTACK OF HISTAMINIC CEPHALALGIA DURING SIMPLE ACID CURVE WITHOUT GASTRIC STIMULANT

FIG. 3



TIMES IN HOURS
HISTAMIC CEPHALALGIA ATTACK WITH SIMULTANEOUS LEVEL OF GASTRIC ACIDITY

FIG. 4

acidity was determined following treatment with histamine and cessation of the attacks of histaminic cephalalgia. This was done following injection of 0.5 mg. of histamine and also following the use of a broth test meal. There were no significant variations between these values and those prior to the use of histamine therapeutically. Histamine consistently produced typical attacks of histaminic cephalalgia prior to use of the drug therapeutically, but produced no headache after treatment.

Although one case is statistically insignificant, these observations indicate that there is more than a casual relationship between histaminic cephalalgia and coincidental duodenal ulcer. Both the history given by the patient and the values for gastric acidity during attacks of cephalalgia are, we feel, confirmatory of this relationship between the two conditions.

It has also been shown by Hay, Varco, Code, and Wangensteen, as well as by other observers, that chronic histamine stimulation will cause peptic ulceration in experimental animals. It is theoretically possible that there is a release of histamine at the time of the occurrence of histaminic cephalalgia, causing a rise of gastric acidity that is instrumental in causing or predisposing to peptic ulceration.

McHardy and Browne reported two cases of Ménière's syndrome treated with histamine that developed duodenal ulcers, apparently as a

result of the chronic stimulation of gastric acidity by histamine. They felt that there was insufficient evidence to justify the use of histamine in the therapy of histaminic cephalalgia with concomitant duodenal ulcer.

All of Horton's cases responded to histamine treatment in so far as the histaminic cephalalgia was concerned, and the peptic ulcers were not slowed but perhaps were accelerated in their symptomatic and roentgenographic healing. This was true also in our case, as there was no apparent adverse effect on the duodenal ulcer during a prolonged series of histamine injections. Prior to and during the treatment with histamine, ulcer therapy was instituted, using frequent milk and cream feedings, a bland low roughage diet, aluminum hydroxide jel, and rest. This resulted in a prompt cessation of symptoms which did not recur following the treatment with histamine. This might be considered an objection to the significance of our results, but it is felt that ours was a patient who would never have had an ulcer if it had not been for the stimulation of the gastric acidity by the histaminic cephalalgia. The ulcer type of therapy utilized served to prevent excessive rise in gastric acidity during therapy with histamine. With ordinary care and treatment of the histaminic cephalalgia it was felt that there would be no recurrence of the ulcer. A point of interest was the effect of histamine "desensitization" on the response of gastric acidity to histamine. In our case there was no apparent change in the response of the gastric secretory apparatus. It would be of interest to follow more such cases to determine if there is a desensitization, at least as far as we can measure by gastric secretory studies.

SUMMARY

1. A case of histaminic cephalalgia with duodenal ulcer is reported.

2. During several attacks of headache the acid curve was high, similar to a curve resulting from the injection of histamine.

3. During periods free from headache, the acid curve showed a low acidity.

4. Following treatment with histamine the headache and the ulcer crater both disappeared with no change in the essential gastric secretory mechanism.

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ASTHMA WITH BRONCHIAL INFECTION TREATED BY PENICILLIN

Preliminary Report

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and
JULIUS L. WILSON, M.D.
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POOR results are commonplace in the treatment of intrinsic asthma. The outstanding successes produced by penicillin in a variety of serious infections naturally have directed attention to the use of this drug in otherwise refractory cases of asthma with bronchial infection. A recent report of the Council on Pharmacy and Chemistry of the American Medical Association reveals that penicillin is effective in staphylococcic, clostridial, hemolytic streptococcic, anaërobic streptococcic, pneumococcic, meningococcic and gonococcic infections. Its efficacy in infections due to Gram-negative bacilli, including Friedländer's bacillus, has not been established. Just as in cases of pneumonia where anatomic diagnoses are being replaced by etiologic diagnoses, the logical treatment of the bronchial infection with asthma is based on identification of the offending organism. In the first case to be presented the predominating organisms found in the sputum were alpha hemolytic streptococci and Friedländer's bacilli.

REPORT OF CASES

Case 1.—Mrs. W. R., a white woman, aged fifty-six years, came to the clinic June 19, 1944, because of hemoptysis, loss of weight and symptoms of chronic bronchial asthma. She had had pansinusitis and bronchial asthma for nineteen years. During the past year she had been having a low grade fever, and since December, 1943, her condition had become progressively worse with a loss of 30 or 40 pounds in weight. During the past year she had had two attacks of hemoptysis. A Caldwell-Luc operation had been performed some years before. On physical examination the patient was found to be quite emaciated but not acutely ill. There were many whistling râles in both pulmonary fields and numerous sonorous râles, especially in the right pulmonary base. Examination of the heart yielded clinically negative findings. A roentgenogram of the chest made on the day of admission showed that the mediastinal structures were distorted by a right dorsolumbar scoliosis but were apparently within normal limits for a person of the patient's age. The hilus shadows revealed no abnormality. The lungs were extremely emphysematous. Areas of infiltration were present throughout the lower four-fifths of the right lung and the middle third of the left lung. The roentgenologist considered that this region was composed of the innumerable closely approximated punctate foci, some of which were so sharply defined and dense as to suggest that they might contain calcium. Confluence of these minute regions resulted in the formation of increased density which uniformly involved the affected portion of the lung. The diaphragm was low and the costophrenic angles blunted. There was, however, no fluid in the base of the pleural cavity. Noted, incidentally, were healing fractures of the lower left ribs in the midaxillary line.

From the Department of Medicine, Tulane University School of Medicine and the Section of Internal Medicine, Ochsner Clinic, New Orleans.

A culture of the sputum on June 19, 1944, revealed the presence of alpha hemolytic streptococci and Friedländer's bacilli. The Wassermann and Hinton tests gave negative results. Routine hematologic studies showed 15.1 grams of hemoglobin, 4,100,000 red blood cells, 8,500 white blood cells with 63 per cent neutrophiles, 9 per cent eosinophiles and 28 per cent lymphocytes. On urinalysis a trace of albumin was found, the remainder of the urinary components being within normal limits. Studies of the blood chemistry showed 29 mg. of nonprotein nitrogen and 87 mg. of dextrose per 100 c.c. Allergic studies confirmed the impression that the patient was suffering from asthma associated with bronchial infection.

The patient had previously had two full courses of treatment with sulfonamides but with little effect. On June 26 the administration of penicillin was started; 20,000 units were given intramuscularly every four hours. After two days, dosage was reduced to 10,000 units every four hours and continued for four days, a total of 480,000 units having been given. This was not considered to be the optimum quantity needed; it was, however, all that was available. A second roentgenogram revealed findings identical with the first. A second sputum culture showed that the predominating organisms were now *Neisseria catarrhalis* and *Micrococcus tetragenus.*

Comment:—The patient showed definite clinical improvement following treatment with penicillin but there was little reversal of the roentgenologic findings. The dyspnea and asthma were ameliorated and the temperature returned to normal. The patient's appetite was also greatly improved. It must be stated, however, that a definite improvement in the patient's outlook preceded the administration of the drug during the first week of hospitalization for study. The amount of sputum brought up was not significantly lessened. The improvement would perhaps have been greater if larger doses of penicillin had been employed but this is doubtful because the predominating flora were completely changed by the treatment. On the basis of this case one must conclude that although penicillin will no doubt be a helpful adjunct in the treatment of asthma due to bronchial infection, it still does not affect the irreversible changes which are characteristic of long standing intrinsic asthma.

Case 2.—Mrs. A. S., a white woman, aged thirty-four years, presented herself August 3, 1944, because of bronchial asthma of two years' duration. Allergic studies showed her to be sensitive to ragweed and house dust. Roentgenogram of the sinuses showed polypoid degeneration of the mucous membranes of the maxillary sinuses. Sinusectomy was performed on August 5 and desensitization begun. The asthma did not improve and by August 21 she had become very much worse. Her temperature rose to 102° F. and continued at approximately this level with diurnal variations of approximately one degree. She was admitted to the hospital on August 23. Physical examination at that time revealed a well developed and well nourished white woman in status asthmaticus. She was coughing up large quantities of thick, greenish-yellow sputum, culture of which showed a predominance of staphylococci and *Str. Hemolyticus (B.).* A roentgenogram of the chest showed three areas of pneumonitis; one in the left upper lobe and one each in the right upper and right lower lobes. The largest of these measured about 5 cm. in diameter and the smallest about 1.5 cm. Routine hematologic studies showed 14,250 white blood cells with 83 per cent neutrophiles, 6 per cent eosinophiles and 11 per cent lymphocytes. Blood chemistry and urinalysis revealed no abnormal findings.

On August 26 she was given 500,000 units of penicillin; this was administered intramuscularly in doses of 20,000 units every four hours. A second roentgenogram made August 31 showed that the two smaller areas of increased density had almost disappeared and the largest one had greatly reduced in size. The character of the sputum was strikingly changed in that the cellularity was considerably reduced; the sputum coughed up following administration of penicillin was clear and translucent though somewhat jellylike in consistency. As in Case 1, the second culture showed predominant organisms to be *Neisseria catarrhalis* and *Micrococcus tetragenus*. During the hospital stay the asthma improved and finally, on September 2, occasional sibilant râles only could be heard.

Comment.—In this second case the patient not only showed definite clinical improvement following treatment with penicillin, but there was in addition clearing of much of the pneumonitis. Again, in this second case the general outlook of the patient was much improved; a certain amount of this may be referable to the use of a dramatic drug. In contrast to the first case where changes in the lungs were irreversible, the second patient was more fortunate in this regard. Asthma, like tuberculosis, must be treated early.

SUMMARY

Two patients with asthma with bronchial infection were treated by the administration of 500,000 units of penicillin each. Both definitely improved, though in the first case irreversible changes in the lungs were unaffected. Penicillin has proved to be a helpful adjunct in the treatment of this type of asthma.

Combined Helium and Epinephrine Therapy

(Continued from Page 190)

4. Portability if desired is possible, and the machine can be operated by attendants with basic instruction.

5. This apparatus can be used for other types of combined inhalation therapy.

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URTICARIA FOLLOWING THE USE OF PROTAMINE ZINC INSULIN

Report of Case

R. F. HUGHES, M.D., F.A.C.A. and H. R. McALISTER, M.B. (Tor.)

Hamilton, Ontario, Canada

Mrs. M. J., aged sixty, has been a diabetic since 1926, at which time she went into diabetic coma. She was discharged from hospital taking regular insulin, 20 units three times a day. She had little or no medical supervision. In June, 1944, when she first consulted us, it was suggested that she be re-balanced, and protamine insulin, requiring only a single daily injection, be used. In ten days this was accomplished, and she left the hospital taking protamine zinc insulin 30 units, and zinc insulin crystalline ten units. In another two weeks it was possible to omit the crystalline insulin entirely.

About a month after the change to protamine zinc insulin, urticaria appeared, first on the feet and ankles, later on the whole body. This urticaria was continually present, was very irritating, and did not yield to local applications.

In order to determine the cause of the condition, samples of various types of insulin were obtained from the Connaught Laboratories, Toronto, through the courtesy of Dr. R. G. Romans. We were informed that the protamine zinc insulin regularly supplied by the Connaught Laboratories is made from a mixture of insulin from beef and pork pancreas. A vial of protamine zinc insulin prepared to contain only insulin from pork pancreas was also supplied. This enabled us to perform the intradermal tests shown in Table I.

TABLE I

	Direct Test	Passive Transfer	
		Sensitized site	Control
1. Protamine zinc insulin (Beef and Pork) (dilution 1:10)	+	+	−
2. Protamine zinc insulin (Pork) (dilution 1:10)	++	++	−
3. Regular zinc insulin (dilution 1:10)	±	−	−

These tests indicate that the patient was sensitive on both direct and passive transfer tests, to both types of insulin containing protamine, but not to insulin in which protamine is not present. One would conclude from this that protamine (salmine) was the cause of the urticaria. Unfortunately, it was not possible to obtain a sterile specimen of salmine for testing.

Treatment in this case presented difficulties, as the patient was obliged to return to her home in the United States, in order to validate her passport. In addition, it was necessary to continue to use insulin as prescribed. Under these restrictions, an attempt was made to carry out skeptophylactic deallergization[1], by having her take ½ unit of regular insulin and of protamine zinc insulin forty-five minutes before her prescribed doses. This was intended to bring about a refractory period, during which the full dose might be given without bringing about the urticarial reaction. However, this was not successful, and was abandoned

after three days trial. A second skeptophylactic method was then tried.[4] This consisted of the administration of protamine zinc insulin in doses of 1, 2, 3, 4, 5, 6, 7, and 8 units (total 36 units) taken at fifteen-minute intervals, followed by 15 units regular insulin, and breakfast. After four days' trial, without result, this was also abandoned, and the conventional treatment was restored.

As a final effort, histamine azo-protein* was given by hypodermic injection in doses of 0.1, 0.15, 0.2 et cetera at three-day intervals, and a prompt and gratifying relief of symptoms was the result. A report was obtained from the patient four weeks later, which indicated that there had been no return of urticaria since the latter treatment had been instituted.

DISCUSSION

Since the introduction in 1936 of protamine zinc insulin, reactions of various types following its use have been reported. These have included local reactions, generalized urticaria and angioneurotic edema. Kern[3] reported a case of purpura following the use of both regular and protamine insulin. Bronchial asthma together with generalized urticaria and angioneurotic edema was observed by Herold[1], in an asthmatic patient under protamine zinc insulin treatment for diabetes.

Local allergic manifestations are very common with protamine zinc insulin. Probably well over 50 per cent of patients complain of an itching or burning sensation at the site of injection, and on the day following an area of erythema is visible, which usually disappears in another twenty-four hours. Invariably these patients require no specific treatment, and within two to three weeks the local reactions entirely disappear. In a comprehensive review of insulin allergy[2] on the basis of animal experiments and clinical observation, it is stated that the protamine fraction may be excluded as an etiological factor in cases of allergy to protamine zinc insulin. However, this case appears to illustrate an unusually prolonged urticarial reaction which was apparently due to the protamine fraction of the insulin in use. This is not unexpected, since many cases of hypersensitivity occur following the use of similar protein or protein components. Schick, in his lecture† to the Fourth Annual Forum of Allergy, stated that it was his opinion that the most common and potent allergens are of embryonic nature (eggs, seeds, nuts, pollen grains, fungus spores). Protamine (salmine), being derived from the sperm of the salmon, is of this nature, and hence it is not surprising that an allergic reaction should occur after parenteral injection of insulin containing this substance.

SUMMARY

1. A case is presented showing an allergic reaction (urticaria) following the use of protamine zinc insulin.

2. Skin tests direct and passive transfer, indicate that the allergen was present in the protamine zinc insulin but not in regular insulin.

*Hapamine, Parke Davis & Co.
†Unpublished.

3. Treatment by specific (skeptophylactic) method was unsuccessful.
4. Relief was obtained with a histamine conjugate (Hapamine, Parke, Davis & Co.).
5. The incidence of protamine zinc reactions is discussed.

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Effect of Beta-Hypophamine and Suprarenal Cortex Extracts on the Prevention of Histamine Shock in the Guinea Pig. Wittich, F. W.: Ann. Allergy, 1:154, 1943.

Guinea pigs of uniform stock and weight were used to determine the lethal dose of histamine and the effect of previous injections of suprarenal cortical extract (Eschatin, each c.c. containing 25 dog units) and Beta-Hypophamine (Pitressin, each c.c. containing 10 pressor units) on the prevention of histamine shock. Animals receiving one dog unit of suprarenal cortical extract subcutaneously and 10 c.c. if physiologic normal saline intraperitoneally three hours preceding lethal doses of histamine showed a delay to histamine shock of an average of one-half hour compared with the controls. They all died however in more violent shock than when treated with histamine alone. Animals, receiving one unit of posterior pituitary pressor extract three hours before receiving a lethal dose of histamine, showed either no evidence of shock or very slight shock.

Clinical observations, as well as these few preliminary animal experiments, would indicate that there is no rational therapy for the use of suprarenal cortex hormone in allergic states.

Posterior pituitary lobe extract, however, seemed to have an antagonistic action to histamine. An epinephrine-pituitrin compound is marketed in the belief that posterior lobe extract prolongs or enhances the action of epinephrine. Clinically the combination is sometimes more effective in asthma than epinephrine alone. This may be the result of an antagonistic action to histamine.

Torantil (Histaminase) in Urticaria, Following Serum Administration. Toomey, J. H., Kriete, F. M., and Epstein, H. C.: J. Pediat. 24:290, 1944.

In their first experiment, the authors gave four tablets of torantil, four times a day, to thirteen patients who developed urticaria following serum administration. There was no change in the duration or severity of the symptoms between these patients and thirteen untreated patients. Similar control comparisons with increased dosage failed to show any material difference between untreated and treated cases. Thirty-six patients with epidemic meningitis, were given torantil as soon as the meningococcic serum was administered in treatment. Twenty-nine cases of epidemic meningitis served as a control. No patients were treated for less than eight days and the treatment was considered as being prophylactic and therapeutic. The authors concluded that Histaminase neither prevents nor ameliorates the serum sickness which follows the administration of meningococcus antitoxin.

Editorial

INSTRUCTIONAL COURSE

The Educational Committee of the College will conduct its next biannual graduate continuation course in allergy at Northwestern University in Chicago. The course will extend from Monday morning, November 5, to Saturday noon, November 10. Lectures and demonstrations will begin at 9 a.m. and will continue until 6 p.m., with a recess of one hour at noon. Registrants may be members or nonmembers of the College. There will be an informal dinner on Monday evening, November 5, in order that the participants may become better acquainted.

Experienced instructors, outstanding in their respective fields, will conduct the courses. Their selection will be based upon the information furnished by the Speakers Bureau of the College and upon their experience in teaching, with an effort to rotate the instructors, when possible, considering those best qualified. The practical, clinically essential features of the various allergic diseases will be adequately presented, keeping in mind the postwar demand for increased knowledge of allergy by physicians in general, when assuming civilian responsibilities. The course will be sufficiently intensive for the advanced physician, wishing to refresh his knowledge of the subject, as well as practical for the newly qualified, desirous of applying proper allergic procedures to their practice.

Chicago, because of its central location, affords an excellent opportunity to medical officers interested in allergy as well as to Canadian physicians. There will be no charges to those in the armed service. The registration fee for others will be one hundred dollars.

All registrants will receive outlines of the courses as well as the revised Manual of Allergy Laboratory and Diagnostic Procedures.

A tentative schedule of the course is herewith presented. The complete course, listing the instructors, will be published in an early issue of the ANNALS. Announcements, including all details, will be mailed in the near future. In addition, announcements will be sent on request.

Registration should be made early, preferably by mail. Hotel reservations should be made in advance. All those wishing to register for this course will please communicate with the Secretary, American College of Allergists, 401 La Salle Medical Building, Minneapolis 2, Minnesota.

At this time the Office of Defense Transportation does not restrict meetings limited to an attendance of fifty. Therefore, it is urged that those contemplating attending the course register early.

If untoward circumstances prevent attendance, the fee will be refunded.

SCHEDULE
November 5-10, 1945
Inclusive

Monday, November 5

9:30	Registration.
10:00–11:30	Fundamentals of Allergy—Immunologic.
11:30- 1:00	Fundamentals of Allergy—Physiologic.
2:00- 4:00	Laboratory and Diagnostic Procedures—General Discussion.
4:00- 6:00	Laboratory and Diagnostic Procedures—Demonstration of Techniques.
7:30	Informal Dinner.

Tuesday, November 6

9:00–11:00	Histopathology of the Allergic Reaction.
11:00–12:00	Materia Medica of Allergy and Pharmacology of Drugs Used in Allergy.
12:00- 1:00	Allergy of the Nose and Paranasal Sinuses—Perennial Allergic Rhinitis (1st session).
2:00- 4:00	Allergy of the Nose and Paranasal Sinuses—Seasonal Allergic Rhinitis (2nd session).
4:00- 6:00	Serum Disease; Allergy from Drug and Biologic Products.

Wednesday, November 7

9:00–10:00	Physiology of Respiration.
10:00–11:30	Bronchial Asthma—General (1st session).
11:30- 1:00	Bronchial Asthma—Therapy, etc. (2nd session).
2:00- 3:00	Dermatologic Allergy—Atopic Dermatitis (1st session).
3:00- 4:30	Dermatologic Allergy—Urticaria (2nd session).
4:30- 6:00	Dermatologic Allergy—Contact Dermatitis (3rd session).

Thursday, November 8

9:00–10:00	Pediatric Allergy (1st session).
10:00–11:00	Pediatric Allergy (2nd session).
11:00–12:00	Pediatric Allergy (G. I. Allergy in Infants)—(3rd session).
12:00- 1:00	Pediatric Allergy (Skin Diseases in Children)—(4th session).
2:00- 5:00	Allergy of the Central Nervous System.
5:00- 6:00	Ocular Allergy.

Friday, November 9

9:00–11:00	Vascular Allergy.
11:00–12:00	Physical Allergy.
12:00- 1:00	Psychosomatic Allergy.
2:00- 3:30	Gastro-intestinal Allergy.
3:30- 4:30	Miscellaneous Allergies—Agranulocytosis (1st session).
4:30- 6:00	Miscellaneous Allergies—Joints, Urinary Tract (2nd session).

Saturday, November 10

9:00- 1:00	General Review and Round Table.

PROBLEMS TO BE CONSIDERED IN THE STANDARDIZATION OF ALLERGENIC EXTRACTS

At the recent meeting of the Board of Regents of the American College of Allergists, Dr. George E. Rockwell, Chairman of the Standardization Committee, gave a report on the progress of the committee.

In discussing the objectives and purposes of standardization, it was brought out in the Letters of the International Correspondence Club of Allergy, recently, that standardization is not of particular interest, but

"clinical dependability and results" are the factors. This seems confusing, for the whole purpose of standardization is just that: namely, standardization makes for consistent clinical dependability and results.

In the Letters the question was also raised why, since house-dust extract can be purified by precipitation with acetone, could not this method be employed for all allergens. Because the method is successful with dust does not mean that it is applicable to all substances. One questions whether milk extract could be so purified.

Purification, while certainly important, will not solve all problems and it alone will not lead to uniformity and dependability. Is there any evidence that even one company's extract is always consistently the same, bottle after bottle, year after year? Unless some method for standardization is developed the allergist has no assurance that he can buy a bottle of a given extract and use it exactly as he did its predecessor. He has no assurance that they are comparable in antigenic properties, activity, concentration and other factors; consequently he cannot be sure of clinical dependability and results.

Standardization of allergens to be successful will undoubtedly have to be done both biologically and chemically. The chemical standardization, if at all possible, should be put on a scientific basis such as normality, molar, oxidation or reduction capacity, et cetera.

Recently, the American Academy of Allergy voted to continue temporarily to use nitrogen as precipitated by phosphotungstic acid as a basis of standardization of pollen extract. At the same time they admitted that there are two or more antigens present in pollen extract, yet they endorsed a method of standardization which gives no information as to the amount of the various antigens present. A method of molar standardization has been suggested which will furnish such information, but apparently it was not even considered. The method itself is simple to use and requires only one more determination than the phosphotungstic acid method. It is only by trial and experiment that its value can be tested, its insufficiencies exposed and improvements made. This means that it will be necessary for allergists all over the country to co-operate in an effort to work out and try new methods if progress along this line is to be expected.

Two experiments of the Standardization Committee were offered to illustrate these points. In the first, a ragweed pollen extract was prepared by Doctor Rockwell which contained identically the same amount of total nitrogen as an extract used by the Army. However, the distribution of nitrogen between large and small molecular antigen was different in each extract. This is shown in Table I.

These extracts were then assigned by Major Halpin to four allergy clinics where they were tested on more than one hundred cases. It was found that the extract labeled Rockwell was considerably more potent than the extract labeled Army; that it gave larger skin tests and in more

TABLE I

Extract	Total nitrogen mgs/c.c.	Army units	Molar Units		
			AMU (major antigen)	BMU (minor antigen)	TMU (total)
Army	0.1000	10,000	892	13,923	14,815
Rockwell	0.1000	10,000	3,062	11,900	14,962

dilute concentrations. From this, it is evident that although two extracts have identically the same amount of total nitrogen, they are not comparable clinically. Therefore, total nitrogen is not a reliable criteria for standardization.

A similar experiment was done using two extracts which were identical in the amount of nitrogen precipitated by phosphotungstic acid, but which were not identical on the molar basis. They proved to be different clinically.

For the second experiment, two dust extracts were made which were identical in total nitrogen; but Extract A contained two and one half times as much precipitable nitrogen as did Extract B. Extract A gave skin tests in higher dilutions than did Extract B. Extract A was then diluted to contain the same amount of precipitable nitrogen as B and this was called Extract C. It gave reactions almost identical to Extract B. This is shown in Table II.

Thus we see that total nitrogen is not a criteria for the standardization of dust extracts, but precipitable nitrogen may be. Experiments are in progress which indicate that although precipitable nitrogen is more reliable than total nitrogen in dust extracts, it is not completely reliable in certain instances and molar standardization will probably be more applicable.

At this meeting the Board of Regents decided to intensify the studies on the standardization of dust extracts. To facilitate this a program was developed which includes three major points. *First*—A series of extracts will be prepared. These extracts will be made from dust collected from all parts of the country which will be extracted, preserved, purified and standardized by various means. *Second*—A committee consisting of Drs. Ethan Allan Brown, Fred W. Wittich and French K. Hansel was appointed to specify definitely the technique, interpretation and reporting of skin tests done on this series of extracts. *Third*—A group of doctors located all over the country will be selected to do these skin tests.

A diligent following of this program will yield sufficient data to be conclusive. It certainly warrants the co-operation and the consideration as well as the conscientiousness of all allergists. We all wish to

TABLE II*

Dust Extract	Nitrogen mg/c.c.	Precipitable nitrogen mg/c.c.	Skin tests on dust sensitive patients done by Dr. Wittich					
			Patient	Dilutions 1:				
				10	100	1,000	10,000	100,000
A	.370	.310	Mrs. B	++	+	+−	−	−
			Dr. C	+++	++	+−	−	−
			A. A.	++++	+++	++	−	−
			Dr. L	++++	++++	++	+	−
			C. S.	++++	++++	++	+−	−
B	.314	.124	Mrs. B	++	−	−	−	−
			Dr. C	++	+−	−	−	−
			A. A.	+++	++	−	−	−
			Dr. L	++++	+++	++	−	−
			C. S.	+++	−?	+−	−	−
C	.148	.124	Mrs. B	++	+−	−	−	−
			Dr. C	+++	+−	−	−	−
			A. A.	+++	++	−	−	−
			Dr. L	++++	+++	++	−	−
			C. S.	+++	++	+	−	−

*Skin reactions were based on measured wheals and areas of erythema.

see this problem satisfactorily controlled, and the only way that this can be achieved is by dividing the responsibility between each and every one of us.

Standardization Committee
Advisory Council
GEORGE E. ROCKWELL, *Chairman*
J. WARRICK THOMAS
FRED W. WITTICH

ORAL DE-ALLERGIZATION OF FOOD HYPERSENSITIVENESS

As indicated in a previous editorial† research in allergy must remain one of the most important interests of the College. New concepts are rightly or wrongly received with utmost skepticism, which, while often well founded, sometimes retards progress. The present generation, to which allergy is an accepted branch of medical science, does not know how the basic ideas of pioneers such as Bostock, Blackley, von Pirquet, Besredka and others in the beginning were ridiculed or even received with hostility.

In our time, too little basic research, particularly along experimental lines, is carried out, partly due, of course, to war conditions. For this

†Research in Allergic Disease, Ann. Allergy, 3:73, 1945.

reason we have approved the publication of a series of papers by Dr. Erich Urbach and his associates, who introduced the concept of de-allergization as an alternative to hyposensitization. On the basis of extensive animal experiments using the Schultz-Dale and the lung perfusion methods as criteria for the presence or absence of antibodies, Urbach postulates that it is possible to "de-allergize" animals highly allergized to proteins by the oral routes, using propetans. These are specific food digests derived from individual food proteins by digestion with hydrochloric acid, pepsin and trypsin. They are free of native protein, rich in proteoses, contain a good proportion of peptones, as well as a small percentage of simpler nitrogen compounds.

Although in Europe the method was tried and advocated by a number of investigators, comparatively few allergists in this country, to our knowledge, have attempted to confirm the procedure, and some have had no success with it. Those of the latter group, who reported negative results, employed their own preparations, whereas the European group used the original propeptans. The editors of the ANNALS suggest an impartial inquiry of the method by experienced allergists, using the original propeptans, particularly by those allergists versed in the scientific study of food allergy.

The investigations should be made upon a sufficient number of definitely known food reactors as well as an equal number of unselected controls which would furnish sufficient statistics and which would be finally convincing of the relative value of the procedure. Urbach's insistence on the proper selection of cases and meticulous supervision of the patient's diet should be given due attention.

A sufficient number of satisfactory case records should be furnished by those undertaking the investigation of propeptans, whether their comments are favorable or unfavorable.

It may be made possible through research funds for those qualified to make the experiments to be furnished with the material for such a study. The results of these investigations, if sufficiently important, may then be published in the ANNALS.

A Note on Cysts and Abscesses Induced in the Rat by the Injection of Oils. Emery, F. E., Matthews, C. S.: J. Lab. & Clin. Med., 28:1795, 1943.

One c.c. of oil was injected intramuscularly in the hind leg of a rat and the site examined two days to one year later for oil, hemorrhage, durability of cyst wall and abscesses. All oils tested (mazola, olive, cottonseed, sweet almond, sesame and peanut) formed cysts. Abscesses were present in nearly one-half of the rats injected with sweet almond oil and in a few with cottonseed oil. Aseptic technique had no bearing on the incidence of abscess formation. With thickness of the cyst capsule as an indicator, sesame oil is more irritating than mazola, olive and peanut oils. All four failed to induce gross inflammation. Sweet almond and cottonseed, therefore, were considered most irritating.

Progress in Allergy

A REVIEW OF THE LITERATURE FOR 1944

Drugs

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Of the 700 papers published during the last year on the subject of Allergy, the following were chosen for their general interest. A good number of the papers not mentioned will be found in the specific subject reviews which are part of this same series and include the fields of Hay Fever, Bronchial Asthma, Atopic Dermatitis, Immunology, Pediatric Allergy, and Chemistry of Pollen. It is assumed that the majority of our readers are familiar with the papers published in the ANNALS OF ALLERGY and in the *Journal of Allergy,* and with few exceptions these also have purposely been omitted.

The general pattern of research in Allergy has changed little in the past year, but, although no major discoveries have been made, a number of problems of moderate stature have been solved and the field of Allergy presents fewer lacunae than it did several years ago.

Sensitivities to the sulfonamides are the subject of a number of papers. Goldschlag[29] reports that the local application of sulfonamides to dermatidites has provoked cutaneous and general sensitivities in about 12 per cent of his patients. He stresses the point that sensitivity to one sulfonamide is usually associated with sensitivity to others and that, in many of his cases, the later application of other drugs provoked a reaction similar to that produced by the sulfonamide. Goldschlag feels, as do many other dermatologists, that the topical application of sulfonamides is contra-indicated whenever other medications will serve the same purpose.

Fisher[20] treated more than 100 patients in whom local or general dermatitis occurred following the local application of sulphanilimide. In twelve of these, oral ingestion of sulphanilamide (0.5 gm.) caused a reappearance of the typical erythematopapular rash seen as a result of the original sensitization.

Lee[42] saw a single prophylactic dose of sulfadiazine (2 gm.) elicit a drug reaction in one hundred and twenty-eight of 25,000 patients. Despite the fact that only a single dose was given, three patients presented a hyperpyrexia accompanied by mental disturbance. In six additional patients, the symptoms lasted for three days for five patients and as long as two weeks for the sixth. In another fifteen patients there was conjunctival injection and a cutaneous eruption, and in one hundred others, mild general reactions which persisted for twenty-four hours.

In a patient reported upon by Koteen[40] a child sensitive to sulfadiazine developed a rash, hyperpyrexia, lymphadenopathy, hepatosplenomegaly, thrombocytopenic purpura and agranulocytosis, following the ingestion of sulfadiazine (9 gm.) of which detectable amounts were still present in the blood twelve days later. The patient recovered, although another patient who developed a similar thrombocytopenia was found to present massive hemorrhages in the adrenal glands, demonstrated post-mortem.

Reed[60] described sulphanilamide as causing convulsions and unconsciousness in a female child and Randolph and Rawling[59], bronchial asthma as occurring in one patient who had had no history of either asthma or allergy and similar symptoms

following the ingestion of sulfadiazine in a patient who had previously suffered from atopic dermatitis, allergic rhinitis, and bronchial asthma. In both patients there was a diminution of vital capacity, and in each a recurrence of symptoms following a second ingestion of the responsible sulphonamide.

In a patient described by Zanfagna[81] there was not only bronchial asthma, but also edema, pruritis, and urticaria. The asthmatic symptoms persisted for ten days.

Abramowitz[2] lists the complications which may follow sulfonamide ingestion as (1) the development of a local or generalized dermatitis, (2) the appearance of photosensitization to ultra-violet radiation, (3) the interference of the action of Roentgen rays, (4) the delay in wound healing time, (5) local sanguineous oozing, (6) interference with the action of sulfonamide compounds by anaesthetics of the procaine series, (7) resistance to sulfonamide therapy, and (8) vulnerability of the patient to subsequent use of the same drug. He feels that the indiscriminate use of sulfonamides is questionable, not only because of the uncertain results but because of the potential hazards listed. His paper, well worth reading in full, reviews the literature pertaining to reactions of sulfonamide therapy and discusses both the histology and pathogenesis of the eruption.

Park[53] tables the reactions of patients to sulphanilamide, sulphapyridine, sulfaguanidine, sulfathiazole, and other sulfonamides. Of the forty patients described, twenty-four reacted only to the individual sulfonamides to which they were initially sensitized. No patient was allergic to more than one of the series without being allergic to them all, as well as to sulphanilic acid. Park concludes that the patient who is sensitive to one sulfonamide may be able to take another but if he is sensitive to two, he is probably sensitive to all. Park's papers on this subject are all well worth reading. In a letter to the *British Medical Journal*[67] treatment with nicotinic acid (50-100 mg.) is described as preventing toxic reactions to sulfathiazole in a patient in whom irritation of the hands, mouth, and anus followed the ingestion of the sulfonamide.

McCormich[49] feels that the improvement in his patient who had a sulfonamide sensitivity was due to the ingestion of ascorbic acid, of which 500 mg. was given daily for a week. The patient was also given oral vitamin B complex. He states that unfavorable skin reactions due to the sulfonamides may be partially related to ascorbic acid deficiency.

Not all forms of treatment with sulfonamides are associated with such sensitivities. Ballenger[6], treated approximately 500 colds with a spray containing ephedrine (2 per cent), the nose then being sprinkled as extensively as possible with sulfathiazole powder. Only three patients developed a skin rash which disappeared within twenty-four hours. Those patients who were known to be sulfonamide sensitive were not treated. The author concludes that although an exact evaluation of the therapy is difficult, the course of the acute infection was shortened and the incidence of complications lessened. Cassady, discussing the paper, was of the opinion that the patients who used sulphathiazole preparations had more nasal congestion and greater irritation than those who use ephedrine alone.

Geiter[26] describes the characteristics and uses of a new salt formed by the chemical combination of neo-synephrine and sulfathiazole. It possesses vasoconstrictor properties comparable to equivalent amounts of neo-synephrine base and approximately the bacteriostatic action as the same quantity of sulfathiazole solution. The material was used in a 1% dilution during the first stages of common colds in several hundred steel workers who used the material twice or three times daily for two days. It was said that only two of the patients progressed to the secondary or muco-purulent stage of naso-pharyngitis. Clinically, there were said to be no symptoms of irritation or sensitivity.

Williams[80] of the Mayo Clinic feels that sulfonamide therapy is useful in acute

sinusitis but that the application of sulfonamides in solution with vaso-constrictors is contra-indicated. He recommends the use of the micro-crystalline sulfonamide suspensions. Weille[78] has used sulfadiazine in the 2.5 per cent solution in 8 per cent triethanolamine as a nasal spray in several hundred patients with no report of irritation or sensitivity.

It is only natural to expect that nebulized solutions of sulfathiazole would be used in the treatment of bronchial lesions. Applebaum[5] experimented with the inhalation of a 5 per cent nebulized solution of sulfathiazole sodium and discovered definite improvement in forty-three of fifty patients suffering from various types of bronchial infections. The patients inhaled approximately 2 c.c. of the solution for twenty minutes, three times daily for ten days. There were two patients who had mild, local, toxic reactions and for these, treatment by nebulizer was discontinued. Oatway[52], on the other hand, treated forty-eight patients with purulent bronchial secretions, with sulfadiazine, sulphamerazine, and sulfathiazole, given orally. In all cases, the sputum was reduced, the average reduction being 62 per cent. The medication was more efficient in simple bronchiectasis than in the presence of atelectasis and putrid secretions. Eleven of the patients had bronchial asthma. In all of the patients the treatment was combined with postural drainage, bronchoscopic aspiration, climatotherapy and treatment of the sinuses.

Reports of penicillin sensitivity are rapidly becoming more numerous, as the drug becomes more widely used. Pyle and Rattner[58] describe a contact dermatitis which occurred in a medical officer who both prepared the various solutions and administered the penicillin to patients. His dermatitis began as a marginal blepharitis and conjunctivitis, and spread to the bridge of his nose, the forehead, and the central portions of his face. Over a period of several weeks eczematous lesions appeared on the hands and penis. As soon as the patient ceased handling penicillin, the eruptions disappeared, recurring as soon as he was re-exposed. Patch tests to penicillin were strongly positive while additional patch tests to the medium, on which the penicillin was cultivated, were negative.

A patient described by Silvers[69] worked as a chemist engaged in penicillin research. He also developed an itchy rash of the eyelids, and the penis, following approximately one year of exposure. A patch test with a pure sodium salt of crystalline penicillin was negative, whereas a similar test with the yellow amorphous form of penicillin sodium was positive. The rash disappeared as soon as direct contact with penicillin ceased.

The patients described by Binkley and Brockmole[11] were physicians administering penicillin to hospital patients. In the first, the eruption appeared on the forehead and lower arms and in the second, was thought to be a seborrheic dermatitis. For the first patient, a patch test with a solution of penicillin containing 5,000 units c.c. was strongly positive. For the second, the patch tests were negative, but an injection of 60,000 units caused pruritis and an eruption of the hands and feet. In both cases, the eruptions ceased when contact with penicillin was avoided. In Barker's patients[9] one, a medical officer dispensing penicillin solutions, the reaction was again an acute dermatitis of the face and neck with vesiculation and a serous exudate of the chin. There was edema of the upper and lower eyelids, subsiding as soon as the patient's occupation was changed. The second patient reported upon in the same paper, responded to penicillin injection with dermatographia and large confluent wheals on the trunk and extremities. On each patient, patch tests reproduced the original lesions.

The patient described by Freyhan[23] developed a severe generalized pruritis for five days, following the administration of 100,000 units of penicillin over a period of ten days. A patient as described by Criep[16] developed a generalized urticaria following the injection of 200,000 units of penicillin over a period of fourteen days.

On this patient, direct intradermal skin tests, passive transfer and precipitin tests were positive to the penicillin drug solution. No anaphylactic antibodies could be demonstrated in the patient's serum to penicillin extract.

Animal experiments by McClosky and Smith[48], using guinea pigs who were sensitized with small daily doses of commercial penicillin, proved sensitivity to be present by both the intracardiac and intravenous injection shocking method and by tests upon the isolated uterus. Sensitization, however, was not uniform in that independently of the doses (5,000-23,000 units) some animals died and others showed no response. The uterine response was often delayed. Desensitization was difficult to demonstrate.

Putney[57] describing the use of penicillin in diseases of the nose and throat, feels that penicillin therapy is the best means of combating infection in these areas. Of nine patients with orbital cellulitis, or brain abscess, only one failed to respond. In chronic osteomyelitis of the frontal bone, lengthy penicillin therapy usually eliminates the necessity for surgery, but in one patient, over 7,375,000 units given over a period of 66 days failed to overcome infection. Acute maxillary sinus infection was cured after several irrigations with penicillin solution. Eight patients with sinus thrombosis adequately treated with penicillin made an uneventful recovery from operation. Used alone, penicillin was disappointing but when combined with adequate drainage as obtained by surgery it effected cure in the majority of patients treated.

Thiamine continues to be the subject of reports on sensitization. A patient treated by Stein and Morgenstern[72] became sensitized so that following the eighth of a series of subcutaneous injections of 30,000 I.U., he suffered for 24 hours from pruritus, dyspnea, and cyanosis. In a patient treated by Mitrani[50] each of six injections with 50 milligrams of thiamine hydrochloride was followed by a maculo-pruriginous eruption of the face, chest and back. Cutaneous tests and passive transfer tests were positive. The patient was successfully desensitized by daily subcutaneous injections, so that eventually he took with no reaction, 100 milligrams daily for ten successive days. Following the course of desensitization, the intradermal tests are said to have become negative.

Reports of dermatitis due to the barbiturates are common but it is comparatively rare to find the condition associated with a progressive anemia. Potter and Whitacre[56] noted a temperature rise and marked erythema covering the entire body following the administration of luminal (1.5 gr.). The next day, following a second dose, the erythema became more pronounced. The patient received Amytal (1.5 grs.) and Aminopyrine (3.5 grs.) which was followed by a chill, with further rise in temperatu e and the appearance of serous-filled blebs covering the entire body. During the next seven days the red cell count declined to 3,000,000 and the hemoglobin to 58%. The skin presented large indurated areas and desquamation. The patient eventually recovered.

For the many plants listed as causing contact dermatitis must be added those to which members of Armed Forces, in their new geographical environments, are being exposed. Hitch[36] describes a severe dermatitis venenata resulting from contact with the Acajou tree (semecarpus atra) which occurs in New Caledonia, the Loyalty Islands, and the New Hebrides group. Nine of ten volunteers who were subjected to study, passed through the typical stages as observed among the patients, the incubation period being two to five days.

Satulsky[64] had previously described dermatitis venenata as caused by the Manzanillo tree with which contact occurs in Panama and the Canal Zone. Harley[33] reports on the severe keratoconjunctivitis and dermatitis due to contact with the Manzanillo tree agreeing with the previous author in stating that effective therapy consists of the prompt use of saline solution. Experiments on rabbits showed that saline irrigation, five minutes after eye contamination, would reduce but did not

prevent the keratoconjunctivitis. On humans, the sap left on the skin for thirty minutes could be removed effectively by ether, soap and water, sea water and lime juice. Oil from the Bhilawanol tree which is related to the cashew nut tree caused an acute dermatitis in sixteen subjects studied by Goldsmith.[31] The patients had come into contact with a mail pouch shipped from India over which the material had been accidentally spilled. Patch tests to the contaminated paper were positive in an unexposed subject. Also from India, Livingood and his associates[46] report on Dhobie mark dermatitis of which there were fifty-two cases in the Twentieth General Hospital, following the wearing of clothes which had been marked with this material derived from the Bella Gutti tree. Patch tests were positive in 80.5 per cent of the subjects, the remainder giving positive tests to marking fluid prepared from the green nuts.

Here at home, Steele and Sawyer[71] remind us of the immediate, severe, generalized urticaria which develops from contact with the brown-tail moth. This insect feeds chiefly on the foliage of apple trees, but is also present in oak, willow, and other common hardwood trees and shrubs. Poisonous material from the caterpillar, the adult moth or the nests coming into contact with human skin produces an urticarial response. Injections at five-day intervals over a period of several months resulted in desensitization.

Two extremely common substances causing allergic reactions are described, first, by Parkin[54] whose patients presented dermatitis due to daffodil juice and second by Sterling and Hollander[73] a case of bronchial asthma due to sensitivity to aspidistra. Tabershay and Skinner[77] report on an eczematoid dermatitis which developed in fourteen of thirty subjects exposed to vinyl carbazole used for impregnating electrical equipment. In another plant all individuals in contact with this material developed a dermatitis within five to fourteen days following exposure.

This last year has brought forward the usual crop of new nasal vasoconstricting agents and the usual reports of the deleterious effects of those introduced the year before. Sternberg[74] reminds us that vasoconstrictors should be used only in nasal sprays and never in the form of drops and should be applied, at the most, once or twice daily preferably when the symptoms are most severe. When used too frequently the mucous membranes become refractory and remain irritated, inflamed, and water-logged. Kully[41] also stresses the point that nasal vasoconstricting preparations have a second dilating effect and that the severity of this secondary congestion is proportional to the frequency with which the preparation is used and the intensity of the vasoconstriction. He also feels that the incorporation of sulfonamides usually causes a severe irritative congestion. He lists the indications for the various medications giving the effect of each on the nasal mucosa and cilia and discussing their therapeutic value.

In 1943, Fabricant and Van Alyea[19] evaluated Privine, which in 104 subjects produced neither local nor general mucous membrane side effects. Gallom[24], however, reported that the use of Privine (0.1 per cent) solution produced toxic reactions in the nasal tissues. In four of his patients, each of whom obtained relief when first using the drug, progressingly increasing amounts were soon required. When the drug was discontinued, the nasal congestion rapidly disappeared of its own accord. The present author's personal experience with Privine corroborates the fact that the patients do require more and more of it as they use it due to the secondary action of the drug itself and not to any exacerbation of the primary allergic condition.

Of fourteen patients treated with local application of Neo-Synephrine by Saltzman[63] a 0.25 per cent solution relieved eight, the remaining six requiring a 1% solution of the drug. In another patient there was a rise in systolic pressure as well as a severe occipital headache, stiff neck, vomiting and profuse perspiration.

Vonedrine (phenylpropylmethylamine) has been the subject of clinical study by

Bumgardner and his associates.[13] They used the substance combined with levulinic acid, Ceepryn and Chlorobutanol in an isotonic solution with a pH of 5.5. The patients, of whom there were 150, suffered either from acute rhinitis, acute sinusitis, chronic sinusitis or allergic rhinitis. The material was used as a spray, as swabs, or as tampons. It was ineffective in allergic conditions. The results were poor in acute or chronic sinusitis. In no patients were there troublesome systemic or side reactions. In our own experience Vonedrine has not given good results in nasal congestion nor has Ceepryn shown itself to be antiseptic.

Stitt[75] on the other hand used the material successfully in 250 patients over a period of forty months. Using a nasal wick technique he reports good results in shrinking the nasal mucosa and opening the ostia of the sinuses. There were no toxic reactions. Vonedrine has also been usd by Glaser[28] in ten cases of bronchial asthma of whom six improved when taking in oral doses (25 mg.) several times daily from five to six months. In seven patients the blood pressure remained constant and in three, decreased. There were no symptoms of central nervous stimulation or disagreeable side effects. The author feels that the drug is as effective as ephedrine and less disturbing than either ephedrine or epinephrine although not as efficient in its broncho-dilating properties as epinephrine.

Marvin[47] used Propadrine pre-operatively in 750 patients, injecting the material subcutaneously in doses of 50 mg. with 2 c.c. of procaine solution (1 per cent). Vasoconstriction is reported to have been satisfactory, the cases including patients who suffered from hypertension, diabetes and heart disease. The drug is said to be more active and less toxic than ephedrine and unlike epinephrine does not cause cardiac irregularities.

Hansel[32] prescribed Nethamine and theophylline isobutanolamine for nasal allergy and bronchial asthma in 200 adults. The drug can be used intramuscularly or intravenously, in severe asthma. Rectal suppositories were also satisfactory. Nausea and vomiting followed oral administration less frequently when the drug was given with food or as an enteric-coated capsule. Whenever the intravenous injection was too rapid there were sensations of heat and burning, fullness of the head and chest, headache and occasional nausea. For the intravenous injection of 50-100 c.c. of the solution at least thirty minutes should be taken.

From England comes the report of a new drug, Pethidine, which, given subcutaneously by Douthwaite[17] in doses of 100 mg., relieved stubborn asthma when continuous treatment with epinephrine had failed. Within a month, Hobbs[37] described the ill effects of the same drug which had been used for persistent urticaria in a patient who treated herself with injections of 50 mg. three times daily for several months. She became excitable, talkative, completely irrational and disoriented. After the drug was discontinued and sedative therapy given, recovery was gradual.

A new drug for the treatment of bronchial asthma is described by Suter and Ruddy.[76] This preparation 1-(3, 4-hydroxyphenyl)-2 amino-1-butanol is said to be as effective as epinephrine in relieving acute attacks of bronchial asthma and yet does not excite the central stimulation nor raise systolic blood pressure. It seems to produce fewer side effects and is approximately one-hundredth as toxic as epinephrine. The diastolic blood pressure is lowered, the pulse rate is increased, the circulation improved without increase in cardiac effort. The dose required is 50 per cent greater than the aqueous solution of epinephrine, 1:1000. On the basis of this work it would seem that a new and effective drug for the treatment of bronchial asthma may soon be available for general use.

The story of Allergosil is now generally known. Smith[70] reported that in 413 patients, an average of three injections of 2 c.c. of the substance, ethylene disulfonate, gave complete relief in 76 per cent and partial relief to the remaining patients representing allergic states. In guinea pigs sensitized to egg albumin, Fisk, Small,

and Foord[22] found that, when three hours before the shock dose, some of the animals were given subcutaneous, intramuscular, or intraperitoneal injections of ethylene disulfonate, the mortality rates were 61 per cent for thirty-three animals treated with Allergosil, 68 per cent for thirty-one animals treated with water and 72 per cent for twenty-five untreated animals. The statistical analysis of these mortality rates showed the differences to be within the limits of standard error. The authors conclude that Allergosil does not protect guinea pigs against anaphylactic shock.

Publicity is still being given to the treatment of bronchial asthma with ascorbic acid. Although previously discussed in this journal, the subject merits brief review. In France, in 1938, Higiesco[35] reported that the intravenous administration of 300 mgs. followed fifteen minutes later by a second injection of 100-200 mgs. of ascorbic acid produced favorable results in sixteen cases of intractable bronchial asthma, only four patients not being benefited by the treatment. In the same year, Hunt[39], in England, gave ascorbic acid orally to twenty-five asthmatic patients daily for eight weeks, five patients receiving massive does parenterally, intramuscularly, and intravenously. There was no improvement in the incidence of attacks or in the general condition, nor was there any diminution in the amount of epinephrine necessary to relieve any attack. In the next year, Cintra[14] reported on twenty patients for whom he considered vitamin C as of considerable value, but Abatte (1) reported that in his patients 100 mgs. or more had no effect, excepting in the presence of vitamin C deficiency.

In 1943, Holmes[38] gave twenty-five patients suffering from ragweed hay fever 100 mg., 200 mg., and 500 mg. amounts of vitamin C during the ragweed season. Five patients were improved within one week while on the first dosage, sixteen showing no relief and serving running controls for the larger doses. Twelve patients improved after one week of 200 mg. taken daily and eight, after three or four days of 500 mgs. taken daily. In all, 88 per cent of the patients were said to have shown improvement. In addition, one asthmatic patient was greatly benefited by 500 mg. daily for two weeks and one eczema patient "almost cured" after one month of daily doses of 150 mg. In the following year, however, Hebald[34] reported on ten patients who were given 250 mgs. of ascorbic acid, twice daily for three or four weeks. Two patients reported slight improvement; eight obtained no benefit.

The effect of the ingestion of large amounts of ascorbic acid taken over a period of several days on skin tests was shown by Newbold[51] to be without significance. In eight male subjects the size of the skin test was unchanged. Engelsher[18] gave 500 mgs. daily to forty-eight patients with both hay fever and asthma. He concludes from his preliminary findings that there is no reason to recommend the ingestion of vitamin C in pollenosis either as the sole measure of therapy or in conjunction with injection therapy.

Bowen[12] treated twenty-five patients with 600 mgs. of ascorbic acid daily and found no improvement as compared to twenty-five other patients who were treated without vitamin C. In the present author's own series (unpublished data), forty-eight patients were given 1,000 mg. daily over a period of two weeks during the height of the ragweed-pollen season. Twenty-three patients stated that they were slightly improved and the remainder that they were slightly worse. It is, of course, possible that only those patients with deficiency states are benefited.

Goldsmith and her associates[30] studied vitamin C nutrition in thirty-two patients of whom twenty-nine had bronchial asthma, two, hay fever, and one, urticaria. A subnormal level of ascorbic acid was found to be present in twenty-one patients. Nine of the patients were put on a standardized regime to determine whether or not they presented an increased need for vitamin C. Six of the seven patients with bronchial asthma were said to be unable to maintain as high a level of the

ascorbic acid as the control group could, under the same regime. In two of the patients the attacks were unaffected although the patients were saturated with ascorbic acid.

Since lowered capillary resistance is said to indicate ascorbic acid deficiency the work of Scarborough and Gilchrist[65] is of special interest. Data obtained from 214 simultaneous determinations did not support this point of view; the lower levels of resistance being found in the subjects with the greater plasma concentration of ascorbic acid.

The difficulties in assessing the papers listed lie in another field of science. The known relationships between calcium, protein metabolism and ascorbic acid have been ignored by almost all of the authors quoted. Crucial experiments definitive in scope and taking all of the various factors into consideration will be required before the true value of ascorbic acid in allergic states can be resolved.

The work with histamine in allergy continues apace. Gant and his colleagues[25] give histamine orally for the treatment of vasomotor rhinitis. It is of interest to note in a paper by Gibertini[27], in 1942, that the saliva contains a large amount of histamine, although very little is present in either bile or gastric juice. It should be interesting to speculate on the mechanism by means of which oral histamine accomplishes its purposes.

The metabolism of histamine is receiving increased attention. The work of Alexander[3] shows that more than 60 per cent of the total amount of histamine present normally in mice is contained in the skin. The substance is excreted in the urine only when histamine concentration in the body is quite high. Whenever the concentration falls below a very definite level, some of the histamine appears in the urine but is evidently cleared through some mechanism other than renal channels. Intravenous injection (3 mg.) results in the excretion of large amounts of histamine in the urine and little in the feces. The histamine content of the blood becomes normal within twenty-four hours.

Those interested in histamine metabolism should read the papers by Anrep and his associates[4], especially for their method for the quantitative estimation of histamine in the urine. They show that histamine can be eliminated both in a free and in a conjugated form. The first, typical of herbivora and the second, of carnivora. In the rat, both forms are present in proportions which vary. The ingestion of meat considerably increases the amount of conjugated histamine excreted. Histamine taken orally is eliminated in the conjugated form for about 5 per cent of the amount ingested. Injected histamine is eliminated in amall amounts as the free form.

Roche e Silva[61], knowing that previous investigators had shown that amino acids such as arginine, histidine and cysteine could block the effects of histamine upon isolated smooth muscle preparations, postulated that the imine group in the amino acids competed with the imine group in the imidazol ring of the histamine for the chemical receptors of smooth muscle. The author synthesized a number of histamine compounds in which the free amine group was combined with the carboxyl group of the various amino acids. These new compounds were devoid of histamine effects and yet were able to block the effect of histamine, added subsequently. The results were consistent with the theory that the pharmacological effects of histamine depended upon: first, the ability of the imine group in the imidazol ring to anchor cell receptors, and secondly, the toxic effect of the free amine radical. The quantities necessary, however (arginine 250 mg. for histamine 1 mg.), would discourage the anti-histamine effectiveness of these compounds in intact animals.

From the clinical point of view, Ruskin[62] has written an interesting and suggestive paper on the therapeutic use of the amino-acid histidine in allergy and shock, remarking on it as a factor in histamine-epinephrine balance. From the

physiological facts available it would seem that histidine treatment had a more rational basis than either treatment with histamine, free or conjugated, or with histaminase.

A measure of the complexity of this subject is seen in the work of Parrot and Richet[55] on the serous exudates of patients with active tuberculosis, acute gastric duodenal ulcers, malignant septic infections and typhoid fever. These workers discovered an organic vasodilating substance which differed from histamine and from acetylcholine. The compound which is more stable than acetylcholine and less stable than histamine produces hypotension and renal vasodilatation in anesthetized cats and dogs. It is soluble in water, ethyl alcohol and amyl alcohol and acetone, and insoluble in ether, chloroform, benzine, and petroleum ether. It is stable in acid and can be stored for several months in a 30 per cent aqueous alcohol solution at room temperature. Half the amount of the substance present is destroyed by human blood serum diluted 1-1-0 at a pH of 7.4 in fifteen minutes at 10° C. The authors state that the new substance described is likely to interfere with the determination of histamine and particularly with that of acetylcholine, since its presence in body liquids may have led to the overestimation of the vasodilator activities of acetylcholine as well as to the inflammation-producing properties of histamine.

Histamine itself is still being used for the treatment of a variety of conditions. Williams[79] treats intrinsic allergy as it affects the ear, nose and throat with subcutaneous injections of 0.1 c.c. of histamine diphosphate solution equivalent to a 1:500,000 dilution of histamine base. Doses given twice a day subcutaneously are increased by 0.1 c.c. each injection until symptoms disappear. A maintenance dose thereafter is 50 per cent of the dose at which improvement took place and average 0.6 c.c. of a 1:10,000 dilution of the histamine base. In some of the patients symptoms return six months after treatment is discontinued. Although some patients can only tolerate as little as 0.1 c.c. of a 1:200,000 dilution initially, no untoward symptoms occurred. The author states that injections of nicotinic acid (25-100 mg.) given subcutaneously in two days; and 100 mg. daily subsequently is as effective in vasomotor rhinitis, as is histamine. Two of his patients, not affected by either drug given alone were improved when both were administered together. In sixteen patients, nicotinamide was ineffective.

Lillie and his colleagues[45] used histamine therapy to improve the hearing of patients suffering from Ménière's syndrome. In twelve of twenty-five patients, the treatment consisted of the daily intravenous administration of a 0.275 mg. of histamine diphosphate in 250 c.c. of saline dextrose or potassium chloride solution given daily for three to six days at the rate of twenty to sixty drops per minute. Histamine was also injected subcutaneously in doses of 0.2 c.c. of a 1:10,000 dilution, increased by 0.05 c.c. twice daily until the patient took 1 c.c., or the optimal dose was reached. Injections were thereafter given daily but the amounts decreased according to the patient's response. In six patients there was marked improvement; in three, a moderate improvement, and in another three, only slight effects. Only three of the patients developed a subsequent increase of deafness. The patients given histamine in potassium chloride solution showed the greatest improvement in hearing, with the tinnitus disappearing in two, and being greatly improved in eight. In ten patients, there was no change. In nineteen patients the vertigo completely disappeared, and in two was greatly improved. In two patients there was no effect. In those patients, in whom symptoms recurred, they reappeared following acute upper respiratory tract infections.

Since histaminase is still being used clinically, a paper by Lemley and Laskowski[44] on the action of this substance, *in vivo,* is well worth notice. They conclude from their work that histaminase in its present state of purity is toxic and that the dose cannot be increased to a level which would protect safely.

With the great interest in histamine azo-protein as a nonspecific method of treatment, mention must be made of the work by Cohen and Friedman[15] on immunity against H-substance. Patients, who, before treatment with histamine azo-protein, reacted to histamine given iontophoretically in a dilution of 1:6,400,000, reacted subsequently to a dilution of 1:200,000-1:1,600,000. These investigators conclude that histamine azo-protein presumably protects against the H-substance released in allergic reactions. Although the authors mention no untoward reactions in the patients treated with histamine azo-protein, in the present author's hands a number of reactions have occurred and similar reactions encountered by other investigators will soon appear in the literature of Allergy.

In this regard it is interesting to note the great gap which exists between clinical papers and the advertising claims based upon them. Hapamine (histamine azo-protein) is presented to physicians as intended for "the treatment of certain allergic conditions in which (1) the allergen is not discoverable, (2) complete avoidance of the allergen cannot be obtained (3) specific treatment with the allergen, in addition to avoidance, fails to restore tolerance levels, or (4) the allergen is of such nature that treatment is ineffective;" in other words, when the allergen cannot be discovered, cannot be used for treatment, cannot be avoided, or when the patient does not improve despite both treatment and avoidance.

It is obviously then no longer necessary to search for the specific causative allergen or having found it either to treat with it or have the patient avoid it. If the material works under these conditions it should undoubtedly work much better when, as in pollinosis, the allergen is known, and when the patient improves with either treatment or avoidance, or both. Since so little treatment is required over so short a space of time one wonders whether, ethically one should use anything else. If Hapamine does what it is claimed to do, treatment with Hapamine will assuredly replace all of our present diagnostic and therapeutic procedures. One eagerly awaits those reports which will certainly soon appear on the results achieved in hay fever. Since the material is also advertised as indicated in "contact dermatitis, physical allergy, urticaria, histamine headache, atopic eczema, vasamotor rhinitis and bronchial asthma" the review of the literature for 1945 should be interesting indeed and well worth waiting for.

Granted that histamine is the causative agent, the work of Lehmann and Young[43] should lead to important clinical data. These investigators discovered that diethylaminoethyldihydroanthracene carboxylate gave sensitized guinea pigs 100 per cent protection against one fatal dose of antigen. Diethylaminoethylxanthene carboxylate was 70 per cent effective. Diethylaminoethylfluorene carboxylate, aminophylline and epinephrine protected only 37 per cent of the sensitized animals. The first product listed above reduces the volume but not the acid concentration of histamine-induced gastric secretion. It intensifies the skin reaction produced by histamine injected intradermally. It reduces the resistance of the pulmonary circulation of the perfused guinea pig's lung as caused by histamine or anaphylactic reaction. It is a more potent broncho-dilator than aminophylline which, the authors suggest, acts beneficially in bronchial asthma because it lowers the resistance of pulmonary circulation.

To return to other forms of treatment, a case report by Fowler[21] presents several interesting facts. Following the removal of the left stellate ganglion, his patient presented a stoppage of the left side of the nose with watery secretion and much sneezing. Ephedrine, epinephrine, and cocaine were ineffective. Atropine sulphate (0.2 mg.), three hourly, had to be discontinued because of the general reaction. On the other hand, Syntropan (100 mg.) given orally three to four times a day, controlled the discharge and had no unpleasant effects. The patient continued with less medication until she was taking 100 mg. daily, continuously ingested over a period of two years.

The treatment of irritative cough of nasal origin by sino-nasal anesthesia is described by Bernfeld[10] who used pledgelets soaked in equal parts of pontocain (2 per cent) and epinephrine(1:1000) applied to the inferior and middle meati for ten minutes. Following this, epinephrine (1:1000) and novocaine solution (1 per cent) were used to infiltrate the tissues submucosally or subperiostally. The anterior and medial walls of the maxillary sinus were flooded with the anesthetic. The treatment, usually repeated, two to four times, gave lasting remission or great improvement.

Although the treatment of severe bronchial asthma is given great attention, surprisingly few references are made to the use of carbon dioxide inhalation. Holinger and his associates (*J.A.M.A.*, 117:675, 1941) found it to be the most effective of all expectorants. Banyai and Cadden[7], evaluating its use over a period of thirteen years state that it changes an excessive but unproductive cough into a useful cough since it liquefies mucopurulent bronchial exudates reducing their viscosity. With the ensuing evacuation of the bronchi, the patient is free from annoying cough for comparatively long periods. The patient is treated for five to fifteen minutes, one to three times daily with 10 per cent carbon dioxide and 90 per cent oxygen set for a flow of four to five liters each minute for the closed method.

The treatment of bronchial asthma of the intractable type is the subject of a detailed paper by Barach.[8] The program for repeated bronchial relaxation consists of aminophylline (0.5-0.7 gm.) instilled rectally with 20 c.c. of water, twice daily for five days and then nightly for three weeks to three months. In refractory patients, 0.48 gm. of the drug is injected intravenously once daily. At intervals of four to eight hours, the patient is given 1 per cent epinephrine or vaponephrin by inhalation and if necessary epinephrine 1:1000 (0.5-1 c.c.) subcutaneously.

Concurrently a saturated solution of potassium iodide in doses of 1 c.c. three times daily is given orally for one week and then 0.3 c.c. twice daily. The patient is also treated with dilaudid 1/20th of a grain daily for four to five days, and if still refractory, is given intravenous glucose (50 per cent) 50 c.c. or 50-90 c.c. of ether in oil rectally. Phenobarbital 0.1 gm. is also given by mouth.

This program is supplemented by the inhalation of helium 75 per cent and oxygen 25 per cent for two hours twice daily. If the patient suffers from chronic bronchitis he, in addition, takes sulfadiazine orally. It would be an interesting study in pharmacodynamics to work out in detail, the actions of each of the drugs given and the methods by which it works. Fortunately, very few patients require such desperate treatment for relief of their symptoms.

Segal[66] used inhalational therapy in forty-nine patients with respiratory disease. Of these, twelve died, eight of whom presented conditions proven by autopsy to have been hopeless as regards treatment. When the patient's chief symptom was anoxia, he was given oxygen. If bronchial spasm predominated he was given helium (70 to 75 per cent) and oxygen (25 to 30 per cent) given under positive pressure. Repeated bronchial relaxation was accomplished by the use of rectal aminophylline, dilaudid, iodides, Neo-Synephrine and Vaponephrin nebulization with adequate humidification. Although Barach[8] finds sulfadiazine given orally more effective than the inhalation of nebulized sulfadiazine spray in Ethanolamine, Segal feels that the ideal technique in a patient with chronic bronchiectasis comprises nebulization with a micro-crystal suspension of sulfathiazole to which may be added iodides in addition to the use of oral iodides. Bronchoscopic drainage is periodically performed.

It may be inferred from this brief general review that each year sees our field become greater in scope and more varied in character. Contributions in the basic phenomena come more and more often from the fields of physics, physiology, immunology, biological and colloid chemistry. Since many of the papers do not appear in journals abstracted from the Cumulative Index, studies of the back-

ground literature must now include Biological Abstracts and the Abstracts of the American Chemical Society. A number of clinical papers, otherwise excellent, are marred by the fact that the authors were apparently not cognizant of the relevant material in the nonmedical literature and neither mentioned it nor took it into consideration. Our clinical papers can approximate the truth and attain permanent value only as they rest as firmly as possible on a solid scientific basis.

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THE Rh FACTORS IN RELATION TO CLINICAL MEDICINE

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In 1940, when Landsteiner and Wiener[10] reported the discovery of the factor Rh of human blood, they opened a new chapter in clinical medicine. In searching for new properties in human blood, they injected the blood of rhesus monkeys into rabbits and obtained antisera which agglutinated the bloods of 85 per cent of white individuals in New York City. The new property in human blood was designated "Rh" (first two letters of the name Rhesus) to indicate the manner in which it had been discovered. Individuals whose red blood cells are agglutinated by the anti-rhesus sera are said to be Rh positive; those whose erythrocytes are not clumped by such sera are said to be Rh negative.

Shortly after the Rh factor was described, Wiener and Peters[26] presented the first evidence of its importance in clinical medicine. They described three cases in which patients receiving transfusions of blood of their own group had severe hemolytic reactions, one of them fatal.

In analyzing the cause of these reactions, they had first to overcome a mental hazard which had retarded progress in this field previously; namely, the rather general conviction that hemolytic reactions could not occur when patient and donor belong to the same blood group.* To establish the diagnosis of intragroup hemolysis several days after a blood transfusion had been given, Wiener and Peters made use of a special technique, designated by them as "differential agglutination." This test, useful whenever post-transfusion hemolysis is suspected, takes advantage of the fact that the agglutinogens M and N are disregarded when selecting donors for transfusions.† If the donor and patient belong to different M-N types, then it is possible to trace the donor's blood in the patient's circulation because the M and N agglutinogens act as natural markers. For example, if the patient belongs to type N and the donor to type M, then after the transfusion the patient's circulation should contain a mixture of bloods of types M and N. Tests of the patient's blood suspension with anti-M serum should show clumps of cells (the donor's type M cells) on a background of unagglutinated cells (the patient's type N cells). If no clumping occurs this proves that the donor's cells have been eliminated and establishes the presence of a hemolytic transfusion reaction.

Having proved by the method of differential agglutination that intragroup hemolysis had indeed occurred in their cases, Wiener and Peters[26] sought the cause of the reactions. By a delicate technique they detected the presence in each patient's serum of an irregular agglutinin which agglutinated a certain proportion of blood suspensions of each of the four groups.** By parallel tests, they then showed that all three agglutinins had identical specificities and gave approximately 85 per cent positive reactions. This suggested that the property responsible for the reactions was Rh, and parallel tests with anti-rhesus sera proved this assumption to be correct. Moreover, all three patients were shown to be Rh negative while the donors responsible for the reactions were all Rh positive.

From the Serology Laboratory of the Office of the Chief Medical Examiner of New York City.

*This belief prevailed even though a number of well authenticated cases had been reported of hemolytic reactions following transfusions of blood of the patient's own group. In a number of cases (Zacho[40], Culbertson and Ratcliffe[4], Neter[21], Levine and Stetson[12]) irregular isoagglutinins were detected in the patient's serum. However, no attempt was made to correlate these observations with one another, and the discovery of the Rh factor finally supplied the key to this transfusion problem.

†M and N are disregarded because they hardly ever give rise to transfusion reactions. Among hundreds of thousands of bloods tested, only 5 have been found with natural anti-M agglutinins, while in two additional cases anti-M agglutinins developed by isoimmunization following blood transfusion; no individual has been encountered in whom anti-N agglutinins were demonstrated with certainty (Wiener[30]). Only a single case of transfusion hemolysis has been traced to the M factor (Broman[2]).

**See footnote, page 230.

Within a year, Wiener[27] collected ten additional cases of transfusion hemolysis due to the Rh factor, and it became clear that at least 90 per cent of intragroup hemolytic reactions could be explained on this basis. For those concerned with blood transfusion, the following facts are important to know:

(1) Natural sensitivity to the Rh factor has never been convincingly demonstrated in man. Therefore, the first transfusion of Rh-positive blood into an Rh-negative patient would not be expected to cause any reaction. This statement holds true universally among males, but there are exceptions in females as is explained below. At any rate, medical officers need not have any concern regarding reactions due to the Rh factor when transfusing wounded male members of the armed forces for the first time.

(2) When Rh-negative individuals are repeatedly transfused with Rh-positive blood a certain number of them will become sensitized to the Rh factor. In these patients transfusion reactions will occur which are usually mild at first (slight chilliness, or rise in temperature), then progressively become more severe, until finally a violent or even fatal hemolytic reaction will result.. Fortunately, the vast majority of Rh-negative patients do not become sensitized despite repeated transfusions; in fact, only one in 25 to 50 Rh-negative individuals are readily sensitized by exposure to the Rh antigen. (This complication will not occur if the transfusions are given at short intervals, because it takes at least 5 to 7 days and usually much longer for sensitivity to develop.) It is obvious, therefore, that whenever transfusion reactions occur, no matter how mild, tests for the Rh factor should be carried out, in order to forestall a more dangerous reaction should it become necessary to repeat the blood transfusions.

(3) In testing for the presence of Rh sensitization, the usual procedure is to examine the patient's plasma for Rh isoagglutinins, as in the original investigations of Wiener and Peters.[26] Wiener[27] soon encountered some cases in which the patients were markedly sensitized, as proved by the occurrence of violent intragroup hemolytic reactions, yet their sera contained no detectable isoagglutinins. These apparently paradoxical cases have now been explained, at least in part, by Wiener's discovery of the Rh blocking isoantibodies.[37] These antibodies are so named because they combine specifically with Rh-positive erythrocytes without producting any visible reaction except that the erythrocytes lose their capacity of being agglutinated even by potent anti-Rh sera, due to blocking of their Rh agglutinogen. In effect, the Rh-blocking isoantibodies "convert" Rh-positive cells into Rh-negative cells. Recent studies suggest that the Rh-blocking isoantibodies are of greater clinical significance than the Rh-agglutinating isoantibodies, and the blocking test is already being used widely as a method of detecting Rh sensitization.

The final test for Rh sensitization is of course the *in vivo* one. Wiener's biological test[28] will be found useful when there is neither time nor facilities for performing Rh tests, and has the advantage that it will also detect sensitization to other blood factors as well. Fifty c.c. of the prospective donor's citrated blood is injected intravenously by syringe, or diluted in saline and given by the gravity method. A sample of the patient's plasma taken 60 to 90 minutes after the injection is compared with a sample of pretransfusion plasma, and if it is not appreciably darker, any amount of blood from the same donor may be given without danger. In positive

**It is remarkable that these irregular agglutinins all reacted best at low temperature. In almost all of the subsequent cases, the agglutinins, when detectable at all, reacted best at body temperature. This apparent paradox has been explained by the recent discovery of the Rh blocking antibodies[37,25], which were present in the sera of the patients studied by Wiener and Peters. According to Wiener, in tests at body temperature, the blocking antibodies rapidly combined with the test Rh-positive cells and prevented the action of the Rh agglutinins also present in the patients' sera. In tests at refrigerator temperature, the blocking antibodies reacted more slowly so that the Rh agglutinins were able to clump the test cells.

reactions, the patient not infrequently has a chill and rise in temperature 50 to 60 minutes after the injection; however, the clinical symptoms are inconsistent and may be mild or absent. In any event, an appreciable increase in the icteric index, e.g., from 3 to 5, is evidence of hemolysis and another donor should be tried.

(4) In analyzing their cases of intragroup hemolytic transfusion reactions, as well as others reported in the literature, Wiener and Peters[26] found that these fall into two well-defined groups: (a) patients receiving repeated transfusions, as already discussed; and (b) patients never previously transfused. In the cases of intragroup hemolytic reactions following an initial transfusion it was invariably found that the patients were females, either pregnant at the time or having had a previous pregnancy. This indicated a second mechanism by which an Rh-negative patient could become sensitive to the Rh factor; namely, by isoimmunization in pregnancy, a phenomenon that had previously been mentioned by Levine and Stetson[12] to explain an intragroup hemolytic reaction observed by them. Since, as Landsteiner and Wiener[11] have shown, the Rh factor is inherited as a simple Mendelian dominant, an Rh-negative woman wedded to an Rh-positive man can have Rh-positive children.* If, during the pregnancy, some of the fetal Rh-positive blood gains access to the maternal circulation, and the woman becomes sensitized in this manner, a subsequent initial transfusion of Rh-positive blood could give rise to a severe hemolytic reaction.

Pursuing the study of isoimmunization in pregnancy further, Levine and his associates discovered another clinical application of the Rh factor, namely, its role in erythroblastosis fetalis.[15] Through the work of Diamond, Blackfan and Baty[6], this disease had been shown to include the syndromes of hemolytic anemia of the newborn, icterus gravis, and hydrops fetalis, as well as certain hitherto obscure stillbirths. As early as 1923, Ottenberg[22] attempted to establish a relationship between heterospecific pregnancy (incompatibility between the blood groups of fetus and mother) and icterus gravis neonatorum, but this hypothesis proved to be incorrect. In 1938, Darrow[5], for the first time, put forward the theory of isoimmunization in pregnancy to account for this disease, but the Rh factor had not yet been discovered, and she incorrectly assumed that fetal hemoglobin was the antigen at fault. When Levine and his associates[3,13] noticed that women who have had pregnancy complications, in particular, stillbirths or infants with erythroblastosis, were also subject to intragroup hemolytic transfusion reactions, the idea occurred to them that the Rh factor might be responsible.

According to the theory of Levine et al.[16], certain Rh-negative women bearing Rh-positive infants become isoimmunized (or sensitized), and the Rh isoantibodies which they produce then filter through the placenta into the fetus and destroy its erythrocytes, giving rise to one or another manifestation of the disease.

This theory was soon shown to be correct when Levine et al.[14], found that, among mothers of erythroblastotic infants, as many as 90 per cent are Rh negative, in contrast to the incidence of only 15 per cent Rh-negative individuals (male or female) in the general population. In addition, whenever the mother was Rh negative, the father and child were Rh positive. Moreover, in about half the cases Rh isoagglutinins could be demonstrated in the maternal serum, proving that she was sensitized to the Rh factor. These observations were quickly corroborated by other workers[23,29], and British investigators[1] reported a much higher percentage of mothers with demonstrable isoagglutinins. In view of the now well-established pathogenesis of the disease, it has been recommended that the name "erythroblastosis" be discarded, and the term "hemolytic disease of the fetus and newborn" substituted. This suggestion

*If the husband is homozygous (genotype *RhRh*) all the children will be Rh positive; if the husband is heterozygous (genotype *Rhrh*) half of the children will be Rh positive and half Rh negative. When the husband and wife are both Rh negative (genotype *rhrh*), obviously all the children will be Rh negative. If both parents are Rh positive, all the children will be Rh positive except when the two parents are heterozygous, in which event ¾ of the children will be Rh positive and ¼ negative.

has been generally adopted, because erythroblastosis is not a consistent feature of the disease, while hemolysis is.

One puzzling observation was the lack of correlation between the anti-Rh agglutinin titer in the maternal serum and the severity of disease in the infant. In some of the most severe cases, anti-Rh isoagglutinins were not detectable in the maternal serum, while at least one case has been reported in which a woman with high-titered Rh isoagglutinins gave birth to an apparently normal infant.[7] These apparent paradoxes have been solved, at least in part, by the discovery of the Rh-blocking isoantibodies referred to above.

Another problem was raised by the fact that families with Rh-negative mothers and Rh-positive fathers and infants occur with a frequency of about 9 or 10 per cent, while hemolytic disease occurs only in one out of 250 to 500 births. Some workers have attributed this to differences in permeability of the placenta to the fetal erythrocytes, but a more reasonable explanation appears to be the differences in the capacity of the mothers to become sensitized. As was already pointed out, only one in 25 to 50 Rh-negative individuals is readily sensitized by transfusions of Rh-positive blood, and the same appears to hold in the case of sensitization by pregnancy. With regard to the exceptional 10 per cent of cases of hemolytic disease in which the mother is Rh positive, these have been largely explained by the discovery of the eight Rh blood types, and the Hr factor, while rare cases appear to be due to isoimmunization against the common blood group factors A, B and O, and possibly even M and P.

The discovery of the role of the Rh factor in hemolytic disease of the fetus and newborn, has resulted in a more rational transfusion therapy of infants suffering from the disease. The use of Rh-negative, instead of Rh-positive blood, has reduced the number of transfusions required to effect a cure, and has saved the lives of the babies who would have succumbed under the older method of treatment.[9,17,20,32] Infants with hemolytic disease should not be allowed to nurse because Rh isoantibodies may be present in colostrum and milk.

While most of the earlier studies on the Rh factor were carried out with antirhesus immune animal sera,* in recent years the tendency has been to employ human sera obtained from Rh-negative mothers of erythroblastotic infants. While only a small percentage of such mothers yield usable antisera, the best human sera give stronger reactions and are easier to work with than the best animal sera. As Fisk and Foord[8] have shown, the antirhesus sera also have the peculiarity that they strongly agglutinate the blood cells of fetuses and newborn, whether Rh positive or Rh negative, and are therefore not satisfactory for testing such blood. The antirhesus sera have the advantage that they all give parallel reactions, identical with original sera of Landsteiner and Wiener, and therefore can be used as standard. The human sera differ in specificity and therefore cannot be used until they have been standardized. This phase of the subject has been clarified by the work of Wiener and his associates[31,33,36,38] on the eight Rh blood types, their serology, heredity and nomenclature.

The most common human anti-Rh agglutinin gives reactions parallel with the standard anti-rhesus agglutinin, and is designated as anti-Rh_0. Two other varieties of human anti-Rh agglutinins have been found; one gives about 70 per cent positive reactions with the blood from white individuals and is designated as anti-Rh′ (Wiener[27]), the other gives about 30 per cent positive reactions and is designated as anti-Rh″ (Wiener and Sonn[34]). With the aid of these three varieties of Rh isoagglutinins, eight types of human blood can be differentiated as shown in Table I. Because of the special position of the factor detected by anti-Rh_0 sera, the eight types fall into

*Sera prepared in guinea pigs proved to give more satisfactory reactions than the original antisera prepared in rabbits. A highly satisfactory antirhesus serum has been prepared by Dr. A. F. Coca in other animals.

TABLE I. CLASSIFICATION OF THE RH BLOOD TYPES

(Wiener[33])

Bloods lacking Rh_o				Bloods containing Rh_o			
Designations of types	Reactions with antisera			Designations of types	Reactions with antisera		
	Rh′	Rh″	Rh_o		Rh′	Rh″	Rh_o
Rh neg.	−	−	−	Rh_o	−	−	+
Rh′	+	−	−	Rh_1 (Rh'_o)	+	−	+
Rh″	−	+	−	Rh_2 (Rh''_o)	−	+	+
Rh′Rh″	+	+	−	Rh_1Rh_2	+	+	+

TABLE II. THE SIX STANDARD RH GENES AND THE REACTIONS WHICH THEY DETERMINE

(Wiener et al.[39])

Designation of genes	Reactions of agglutinogens with antisera			
	Rh′	Rh″	Rh_o	Hr
rh	−	−	−	+
Rh_o	−	−	+	+
Rh′	+	−	−	−
Rh_1	+	−	+	−
Rh″	−	+	−	+
Rh2	−	+	+	+

four natural pairs, giving rise to what amounts to a double scheme of four types each, analogous serologically and genetically to the four common blood groups. (Incidentally, this considerably simplifies the task of learning and remembering the scheme of the Rh blood types.) In general, the types are named after the antisera with which they react. Blood reacting with anti-Rh_o and anti-Rh′ are designated Rh_o' or more simply and preferably Rh_1, instead of Rh_oRh', because genetic studies have shown this property to be due as a rule to the action of a single gene Rh_1 which produces a single agglutinogen, but reacts with two antisera just as A_1 blood reacts with both α_1 and common α agglutinins. This same explanation applies for the designation of type Rh_2. Types Rh′Rh″ and Rh_1Rh_2, on the other hand, are so named because they result from the combination of a pair of allelic genes (cf. Table III).

Of the three factors, Rh_o is by far the most antigenic, Rh′ is less antigenic, while Rh″ is the least antigenic. Individuals of types Rh′, Rh″ and Rh negative are therefore most apt to have intragroup hemolytic transfusion reactions and erythroblastotic infants. Type Rh_1 individuals may rarely become sensitized to the Rh″ factor in bloods of types Rh_2 and Rh_1Rh_2, while type Rh_2 individuals have rarely become sensitized to the factor Rh′ in bloods of types Rh_1 and Rh_1Rh_2, thus accounting for some instances of Rh sensitization in Rh-positive individuals. Obviously, such patients may be transfused either with blood of their own Rh type or Rh-negative blood, because Rh-negative individuals hold the same position in the scheme of the Rh blood types as group O individuals in the scheme of the four common blood groups.[35]

An important cause of intragroup sensitization in Rh-positive individuals is the Hr factor. This property was first described by Levine and Javert,[18] who detected

TABLE III. THE EIGHT RH BLOOD TYPES, THEIR DISTRIBUTION AND THE RELATION TO THEM OF THE HR FACTOR
(Wiener et al.[39])

Rh blood types	Distribution among (per cent)		Reactions with antisera			Geno-types	Reactions with anti-Hr serum
	Whites	Negroes	Rh′	Rh″	Rh_o		
Neg.	12.9	8.1	Neg.	Neg.	Neg.	*rhrh*	Strong
Rh_1	54.1	20.2	Pos.	Neg.	Pos.	Rh_1Rh_1 Rh_1Rh'	Neg.
						Rh_1rh Rh_1Rh_o $Rh'Rh_o$	Weak
Rh_2	16.0	22.4	Neg.	Pos.	Pos.	Rh_2Rh_2 Rh_2Rh'' Rh_2rh Rh_2Rh_o $Rh''Rh_o$	Strong
Rh_1Rh_2	13.2	5.4	Pos.	Pos.	Pos.	Rh_1Rh_2 Rh_1Rh'' $Rh'Rh_2$	Weak
Rh_o	2.6	41.2	Neg.	Neg.	Pos.	Rh_oRh_o Rh_orh	Strong
Rh′	0.9	2.7	Pos.	Neg.	Neg.	$Rh'Rh'$ $Rh'rh$	Neg. Weak
Rh″	0.3	—	Neg.	Pos.	Neg.	$Rh''Rh''$ $Rh''rh$	Strong
Rh′Rh″	0.01	—	Pos.	Pos.	Neg.	$Rh'Rh''$	Weak

in the serum of an Rh-positive mother of an erythroblastotic infant an agglutinin which acted on all Rh-negative bloods and all Rh-positive bloods which did not react with anti-Rh′ serum. Because the property is present in all Rh-negative bloods it was designated Hr (the opposite of Rh). The nature of the Hr factor has been clarified by the work of Race and Taylor[24] who showed that it was present in the agglutinogens determined by genes *rh, Rh_o, Rh_2 and Rh″*, but absent from the agglutinogens determined by genes Rh_1 and *Rh′* (cf. Table II). Race and Taylor's theory has recently been corroborated by statistical studies of Wiener et al.[39], and the implications of the theory are summarized in Table III taken from the paper of Wiener et al. In cases of erythroblastosis due to Hr sensitization, the mother is Hr negative, and the father and child Hr positive. Hence, the mother must belong to type Rh_1 (genotype Rh_1Rh_1 or, rarely, genotype Rh_1Rh') or extremely rarely to type Rh′ (genotype *Rh′Rh′*). Despite statements to the contrary[19], the child can never be Rh negative (or belong to types Rh_2, Rh_o or Rh″), because it must inherit one Rh_1 or *Rh′* gene from the mother. There is no restriction as to the type of the father because Hr-positive individuals may occur in all eight Rh blood types.[39]

Obviously, an up-to-date blood donor service will eventually have to include a panel of Hr-negative donors as well as Rh-negative donors. Before transfusing sensitized Rh-positive individuals who belong to type Rh_1, a biological test with Hr-

negative blood should be tried. The same procedure may be followed when transfusing erythroblastotic babies with Rh-positive mothers of type Rh_1. The simplest and safest method of treating erythroblastotic infants with Rh-positive mothers, however, is to transfuse the mother's washed erythrocytes suspended in saline or compatible plasma, provided the mother is well enough to act as donor.

It is evident that the discovery of the Rh factor has supplied the key to an intricate field of considerable clinical importance. There is no doubt that there is still much of fundamental importance to be learned concerning this intriguing subject.

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Histamine

Histamine Tolerance. Katzenstein, R.: Yale J. Biol. & Med., 16:325, 1944.

By the daily repeated intravenous injection of increasing quantities of histamine, tolerance to the drug can be developed. The author demonstrates this in describing his work with dogs. Increased tolerance to histamine for the dog is not associated with adrenal cortical hypertrophy. Nontolerant controls show lesions of the central nervous system, gastro-intestinal tract and spleen. These are believed due to the acute hypotension and the inefficiency of the circulating blood volume.

News Items

Recently, Dr. Irving W. Schiller, Boston, a Fellow of the College, presented the Research Fund with contributions from grateful patients—Mr. A. J. Rahnovitz, Mr. Nathan H. Friedman and Miss M. Karas.

At the May meeting of the Pittsburgh Allergy Society, the following scientific program was presented: "Lens Protein Sensitization," Dr. A. R. McCormick; "Contact Dermatitis," Dr. A. Harvey Neidorff; group discussion of "High or Low Dosage Therapy in Inhalant Allergy," led by Dr. John E. Gordon.

Dr. James A. Mansmann, a Fellow of the College, is secretary of the Society.

Dr. Leon Bentolila of Buenos Aires, Argentina, and Dr. Arturo Mardones, Santiago, Chile, Fellows of the College, who were engaged in postgraduate studies at Doctor Rowe's clinic at Oakland and San Francisco, have returned to their native countries to resume their practice of allergy.

Dr. Ulysses Fabiano Alves, Jr., Rio de Janerio, an Associate Fellow of the College, who has completed studies at the Mayo Clinic and New York Hospital, is at the present time doing special work in allergy at the Vaughn Memorial Clinic under the direction of Dr. J. Warrick Thomas.

Professor E. C. Stakman, an Honorary Fellow of the College, and Chief of the Division of Plant Pathology and Botany of the Department of Agriculture at the University of Minnesota, has returned from Mexico City where he has been making special studies in plant pathology. On his return, he made rust surveys throughout the central portion of the United States.

Dr. Frank G. Crandall, an Honorary Fellow of the College, has been discharged from the Army and has established offices at Los Angeles, California, in the Wilshire Professional Building, 3875 Wilshire Boulevard. His practice will be limited to allergy. For three years Doctor Crandall served on active duty in the Pacific area as Colonel in the Medical Corps.

The University of Illinois College of Medicine announces its sixth semi-annual Refresher Course in Laryngology, Rhinology and Otology, September 24 through September 29, 1945, at the College, in Chicago. The course is intensive and largely didactic, but some clinical instruction is also provided.

It is especially suited to specialists unable to devote a longer period for advanced instruction and to others seeking a comprehensive review of the field of otorhinolaryngology. The number of registrants will be limited. It is therefore desirable to apply for registration immediately. The fee is $50. When applying, give full details as to school and year of graduation, postgraduate training, college degrees, etc. Write to Dr. A. R. Hollender, Chairman, Refresher Course Committee, Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Illinois.

The College gratefully acknowledges the second gift of $300 made by the Allergen-Proof Encasings, Inc., Cleveland, Inc., Cleveland, Ohio, for purposes of scientific research and investigation in the field of allergy.

This fund will be applied towards the College fellowships now established at the Mayo Foundation and in the Department of Biochemistry of the University of Cincinnati.

NEWS ITEMS

A grant of $200 has been made by the Hollister-Stier Laboratories, makers of allergens, to The Committee of Allergists for the Study of the Unknown Causes of Hay Fever. This sum is to be used for research purposes by the Committee as it sees fit when attempting to solve what is commonly known in the South as the "X hay fever" problem.

A history and description of the condition, as well as the areas involved, are very adequately discussed in Wodehouse's recent book "Hayfever Plants," Chronica Botanica, Waltham, Massachusetts, 1945.

Almay, Incorporated, manufacturers of hypo-allergenic cosmetics, has contributed to the Educational Committee of the American College of Allergists a fund of $500 for the year 1945, to be used by the Committee for undergraduate teaching, as it sees fit. The Committee and the Board of Regents, when accepting this contribution, acknowledge their gratitude for this generous grant. The Committee will use this fund for undergraduate teaching in allergy where it considers it will do the most good.

COLLEGE RESEARCH FOUNDATION

In the November-December, 1943, issue of the ANNALS OF ALLERGY an announcement was made of the establishment of a College Research Foundation, since it was thought best to have the College members initiate the first fund to be used for research in allergy. A plea was made that 100 Fellows of the College, who are able and willing to do so, contribute $50 each towards the Fund, such contributors to constitute an honor roll. Although the amount of $50 was an arbitrary sum, some contributed more and others less towards this Fund. At that time it was also stated that personal solicitation would be avoided as much as possible. There was a very ready response at the beginning, but since no more notice has been given to this Fund and several hundred more members have been taken into the College, we think that it is fitting to announce the names of those who have made such contributions. Some of the members generously responded with more than double the amount requested. These were some of the instructors who participated in the instructional course at St. Louis and who turned over the amount of their expenses to the College.

With considerable funds still needed for the Fellowships established at the Mayo Foundation and the University of Cincinnati, we are appealing to those members of the College, who are able to do so, to send in their contributions. These funds are deposited in a separate account of the College and will be used in payment of the two fellowships that have been established or for other research, and then only upon the direction of the members of the Board of Regents and the President of the College.

Incidentally, an audit of all funds of the College is presented to the Board of Regents at each of its meetings. Every member in the College has received a statement of the financial condition of the College as of September 30, 1944 (prepared by a certified public accountant), and will receive the same this year.

Those who have contributed to this College Research Foundation are: Dr. W. Byron Black, Kansas City, Mo., Dr. Ralph Bowen, Houston, Texas, Dr. Norman W. Clein, Seattle, Wash., Dr. John P. Henry, Memphis, Tenn., Dr. Florence M. Kline, Pittsburgh, Pa., Dr. Delbert J. Parsons, Springfield, Ohio, Dr. Homer E. Prince, Houston, Texas, Dr. Harry L. Rogers, Philadelphia, Pa., Dr. Ralph H. Spangler, Philadelphia, Pa., Dr. Orval R. Withers, Kansas City, Mo., Dr. Fred W. Wittich, Minneapolis, Minn. This list does not include the generous donations already made by commercial groups and other friends of the College, which have already been announced in these columns.

NEWS ITEMS

Dr. G. Estrada de la Riva of Havana, Cuba, an Active Fellow of the College and editor of the Spanish supplement, published by the College, has been appointed Professor in Allergy for an extension course to be presented at the University of Havana this summer. Although these postgraduate courses have been held the past four years, this is the first time that allergy has been given consideration enough to be included. Doctor de la Riva is Associate Professor of Experimental Pathology at the University.

ANNOUNCEMENT

At the recent meeting of the Board of Regents, held at Cleveland June 2 and 3, it was decided that the Questions and Answers department of the ANNALS be resumed since there have been many requests that it appear. Members are urged to submit any questions which may arise in their practice of allergy, which will be referred to the best known authorities for reply in the ANNALS. It is not necessary that the queries be signed other than "M.D." and the name of the state mentioned.

The New and Unused Therapeutics Committee of the College is now functioning. Dr. Ethan Allan Brown is Chairman of this committee, and Drs. Philip M. Gottlieb, George E. Rockwell, Frank A. Simon and Erich Urbach have been appointed to serve on the same. It was decided that a page headed "New and Unused Drugs" be included in the ANNALS, in which articles will be published which will be signed by the member of the committee making the report or by the Chairman of the committee. The literature concerning important drugs will be reviewed and the drugs given a trial, when feasible. Members are asked to submit questions concerning drugs. Certain preparations about which there has been some controversy will be investigated.

BOOK REVIEWS

THE SPECIFICITY OF SEROLOGICAL REACTIONS. By Karl Landsteiner, M.D., The Rockefeller Institute for Medical Research, New York. Price, $5.00. Cambridge, Mass.; Harvard University Press, 1945.

Landsteiner succeeded in finishing all but the final writing of the revision of his opus magnum before final illness put an end to his labors. Thus, the man who, more than anyone else, contributed to make immunology an integrated part of science, leaves us, like a testament, his views on the status of immunology and the avenues of further progress. Landsteiner presents in Brueghelian detail all the infinitely varying aspects of the subject. The book is replete with references to the original papers or, where such references became too numerous, with quotations of reviews or other publications where details on literature can be found. The mellowness of viewpoint and richness in detail makes this book an invaluable companion for the immunologist. It is, however, no longer—as were the previous editions—a book the beginner will enjoy reading as an introduction to immunology.

The chapters on chemospecificity and on supersensitivity to simple substances are of particular importance to those who are interested in the basic aspects of allergy. They provide a most valuable guidance to the critical appraisal of experimentation in our field. Not every allergist will agree with Landsteiner's viewpoints on the interrelations of allergic phenomena and anaphylaxis, but that will not impede the profit the reader will derive from the example of a sober and thorough analysis of factual knowledge at hand. With Landsteiner, we lost one of the very few who are able to unite in one person the chemical, immunological and medical experience which alone will guide us safely through the confusing perplexity of our problems. The progress in our field will depend more and more on the co-operation of the chemical and the immunological technologist with the clinician. For those who strive for the integration of experimental and clinical observation, Landsteiner's book will remain a spiritual guide for a long time to come.

A. J. Weil.

PRINCIPLES AND PRACTICES OF INHALATIONAL THERAPY. By Alvan L. Barach, M.D., Associate Professor of Clinical Medicine, Columbia College of Physicians and Surgeons; Assistant Attending Physician, Presbyterian Hospital. 315 pages. 51 illustrations. Price $4.00. Philadelphia: J. B. Lippincott Company, 1944.

This book is intended as a guide to physicians responsible for the technical procedures used in inhalational therapy and those who wish to understand the physiologic basis for the same. The author, a pioneer in developing the practice of inhalational therapy, has compiled in a clear and concise manner a handbook on the methods of inhalational therapy in considerable detail. The importance of inhalational therapy is becoming widespread. Modern medical practice is applying it in heart failure, coronary artery disease, postoperative atelectasis, new born atelectasis, pneumonia, pulmonary edema, emphysema, bronchial asthma, cerebral thrombosis and pulmonary infarct, as well as the treatment of war gas poisoning severe hemorrhage, altitude sickness and shock.

The pathologic physiology of respiration of the various clinical entities considered determines both the specific indication for treatment, as well as the selection of the method of inhalational therapy. These methods, are briefly but clearly de-

tailed so that the physician may be guided to the selection of the proper apparatus and the employment of the most efficient method when carrying out this form of therapy. Technicians and nurses who carry out the detailed procedures of inhalant therapy may also find the clinical factors in the book very valuable.

Each chapter is followed with an adequate essential bibliography. There are thirty-eight chapters beginning with the historic and physiologic background of inhalational therapy and including the therapeutic use of oxygen, carbon dioxide, helium, and the use of positive pressure and vaporized solutions of epinephrine and neosynephrin. The second chapter defines and presents the causes, as well as the pathologic physiology, symptoms and inhalational therapy of acute altitude sickness and acute anoxia. The treatment of pneumonia, coronary thrombosis and coronary sclerosis, shock, pulmonary infarction, massive collapse, postoperative atelectasis are clearly presented in succeeding chapters.

Chapter 11 on "Bronchial Asthma" is of particular value to allergists. The disease in relation to inhalational therapy is clearly defined. The pathologic physiology with particular reference to the physical advantage of helium-oxygen mixture over air is given in detail, with studies in vital capacity, as well as the use of aminophyllin therapy in conjunction with helium-oxygen inhalation in patients with intractable asthma which is of extreme practical value to any physician in treating acute asthma.

In order to appreciate the number of diseases benefited by inhalational therapy the following conditions are enumerated which are adequately discussed: obstructive lesions in the respiratory tract, pulmonary emphysema, accidental asphyxia, hemorrhage, peripheral arteriosclerosis, migrain, seasickness, gas gangrene, tetanus, anesthesia, anoxia and brain lesions following fever therapy, head injuries, paralysis of the respiratory musculature, cerebral embolism and thrombosis, chronic pulmonary tuberculosis, blast injuries of the lungs, aerial transportation of diseased patients, oxygen poisoning and submarine medicine and caisson disease.

The final chapters are given over to the methods of inhalational therapy with the illustrations of mechanical devices used, detailed procedures, et cetera, with the various diseases mentioned.

This book is the last word in the therapeutic uses of gases and clinical medicine, and no doctor in private practice or member of a hospital staff should be without it.

F.W.W.

Experimental Approach to Oral Treatment of Food Allergy

(Continued from Page 186)

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